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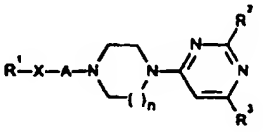
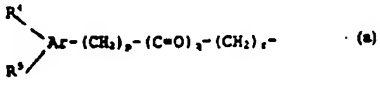


(I)



(a)

(57) Abstract

The invention refers to novel pyrimidine derivatives of formula (I), wherein R^1 stands for a group of formula (a), wherein Ar means an aromatic homocyclic group, R^4 and R^5 represent hydrogen, halogen, hydroxy, alkyl, optionally substituted alkoxy, alkylthio group and oxidized derivatives thereof, optionally substituted amino, carboxy and derivatives thereof, sulfo and/or sulfonamido; and p, q and r are 0 or 1; R^2 and R^3 stand for amino; or a moiety derived from a nitrogen-containing heterocycle; X means a single bond; an optionally oxidized sulfur atom; or an optionally substituted nitrogen atom; A stands for an optionally substituted alkylene group; and n is 1 or 2. The invention relates also to a process and the intermediates for the preparation of the compounds of formula (I). The compounds according to the invention possess a remarkable lipid peroxidation inhibiting effect which is detectable both under *in vitro* and *in vivo* conditions. Thus, these compounds are useful for the prevention and/or treatment e.g. of injuries of the head, brain and spinal cord; as well as tissue damages arising from ischemia (including e.g. reperfusion injuries), myocardial infarction or coronary heart disease.

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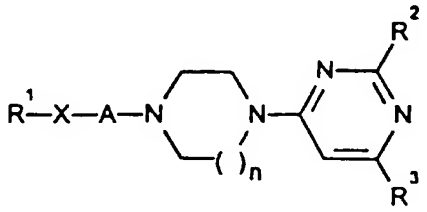
PYRIMIDINE DERIVATIVES

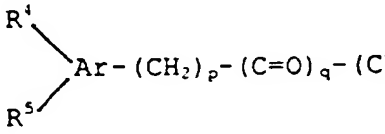
This invention relates to novel pyrimidine derivatives capable to effectively inhibit the peroxidation of lipids. More particularly, the invention refers to novel pyrimidine derivatives of formula (I),



(I)

wherein

R^1 stands for a moiety of formula (a)



(a)

wherein

Ar means a C_{6-10} aromatic homocyclic group,

R^4 and R^5, independently from each other, represent hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, nitro, C_{1-4} alkanoyl, optionally substituted amino, carboxy, C_{1-4} alkoxycarbonyl, carboxamido, cyano, sulfo and/or sulfonamido; and

p, q, and r are, independently from each other, 0 or 1;

R^2 and R^3, independently from each other, stand for amino; or a moiety derived from a 5-8-membered saturated heterocycle containing at least one nitrogen atom;

X means a single bond; a sulfur atom optionally substituted by one or two oxygen atom(s); or an optionally substituted nitrogen atom;

A stands for a straight or branched chain C_{1-4} alkylene group optionally substituted by halogen, hydroxy, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkanoyloxy, optionally substituted amino and/or oxo; and

n is 1 or 2,

with the proviso that when

R^1 means a moiety of formula (a), wherein

Ar means phenyl; and

at least one of R^4 and R^5 stands for halogen, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-4} alkanoyloxy or methanesulfonyloxy;

A may not be unsubstituted C_{1-4} alkylene; and

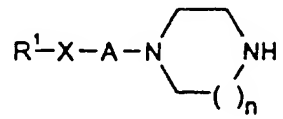
with the further proviso that when

R^1 is 2,5-dihydroxybenzoyl;

A may not be alkylene substituted by oxo;

as well as their salts and pharmaceutical compositions containing these compounds.

The invention refers also to a process for the preparation of the above pyrimidine derivatives. The novel intermediates of formula (II)



(II)

used in the synthesis of the compounds of formula (I) also fall within the scope of the invention.

It is known that the peroxidation of lipids of the living organism is a metal ion-catalyzed radical process,

in which oxygen-containing radicals (e.g. hydroxyl radical, superoxide anion being radical in character and the like) also participate. This process alters the cellular membranes, interferes with the membrane transport processes and finally, it may lead to the death of cells. Lipid peroxidation plays an important role in a number of pathological conditions and diseases and even in ageing. Such diseases and conditions are e.g. the injuries of the brain and spinal cord, acute cerebral stroke, some types of cerebrovascular spasms, tissue damages arising from ischemia (especially the so-called reperfusion injuries occurring during and after restoration of blood circulation), myocardial infarction, coronary heart disease, atherosclerosis, inflammatory diseases such as rheumatic arthritis or some inflammatory diseases of the gastrointestinal system, e.g. pancreatitis or ulcerative colitis; furthermore autoimmune diseases, certain side-effects of drugs, asthma; as well as several chronic diseases of the nervous system, e.g. parkinsonism, Alzheimer's disease and the like [see e.g. B. Halliwell: FASEB J. 1, 358 (1987); J.M. Gutteridge and B. Halliwell: Methods in Enzymology **186**, p. 1-84 (1990); D. Salvemini and R. Botting: Drug News & Perspectives 6, 274 (1993)].

An intensive research is being carried out worldwide to find, on the one hand, substances which moderate or inhibit oxidative processes in the living organism in general (antioxidants) and, on the other hand, active agents specifically preventing the peroxidation of lipids. This latter type of active agents can be used in mammals, including man, for the prevention or treatment of diseases and conditions such as those mentioned above as being related to lipid peroxidation processes. These

drugs may have an outstanding therapeutical importance: active agents with lipid peroxidation inhibitory activity that are suitable to treat e.g. injuries of the central nervous system can be considered as life-saving drugs [see e.g. J. Lehman: Drug News & Perspectives 5, 252 (1992)].

Several endogenous substances inhibiting lipid peroxidation, e.g. alpha-tocopherol (alternatively named vitamin E) are present in the internal regulatory system of the mammalian body [see, e.g. M. J. Kelly in: "Progress in Medicinal Chemistry", vol. 25, p. 250, eds. G.P. Ellis and G. B. West, Elsevier Science Publisher (1988)]. The importance of substances inhibiting lipid peroxidation is illustrated e.g. also by two studies involving more than one hundred thousand people, according to which the risk of some diseases such as coronary heart disease can be reduced by the regular intake of vitamin E [M.J. Stampfer et al.: The New England Journal of Medicine 328, 1444 (1993); and E. B. Rimm et al.: The New England Journal of Medicine 328, 1450 (1993)].

The objective of the present invention was to find novel synthetic pyrimidine derivatives, which effectively inhibit the lipid peroxidation and are consequently useful to treat certain diseases and conditions in mammals, including man, where the inhibition of lipid peroxidation is desired.

Now, it has been found that this requirement is met in an outstanding manner by certain pyrimidine derivatives bearing two optionally substituted amino groups, where the pyrimidine ring is attached to a nitrogen atom of a piperazine or homopiperazine cycle and the other nitrogen of said piperazine or homopiperazine cycle bears a

moiety, which comprises a naphthyl or phenyl group in a bond system defined hereinafter in detail.

A number of compounds with structures resembling to some degree the structure of the compounds of the present invention are described in the literature. For instance, some compounds are known, wherein one of the nitrogen atoms of a piperazine ring is attached to an open-chain or cyclic hydrocarbon group whereas the other nitrogen atom thereof bears a 6-membered nitrogen-containing heterocycle such as a substituted pyridine, pyrimidine or triazine ring. These known compounds show a variety of biological effects.

One important class of these known compounds is represented by substances wherein the group derived from the above-mentioned heterocycle containing one or more nitrogen(s) is e.g. a pyridinyl, pyrimidinyl or triazinyl group bearing optionally substituted amino group(s) [such as the 2,6-di(substituted amino)-4-pyrimidinyl moiety occurring also in the compounds of the present invention). Simultaneously, said hydrocarbon group of these compounds may be varied within a wide range: it may be e.g. a group with a steroidal skeleton (see the PCT patent applications published under Nos. WO 87/01706 and WO 87/07895); a group with a secosteroidal skeleton (PCT patent application published under No. WO 88/07527); various substituted alkyl groups of medium chain length; as well as various mono- and bicycles, e.g. substituted phenyl, phenoxyalkyl or benzopyranyl groups and the like (PCT patent applications published under Nos. WO 88/08424 and WO 91/06542). These classes of compounds were reported to have lipid peroxidation inhibitory effect. It should be noted here that no molecules containing a naphthyl or

benzyl group or a benzoyl group attached through a nitrogen or sulfur atom occur among these known compounds. The said PCT patent application published under No. WO 88/08424 disclosed some compounds resembling to one type of the compounds of the present invention, these known compounds contain a nitrogen heterocycle attached to a piperazine ring nitrogen while the claimed scope of the groups attached to the other nitrogen atom of the same piperazine ring include among others 2,5-dihydroxybenzyl or substituted benzoylamino both being connected to the piperazine ring via a C_{2-4} alkylene chain. In the specific compounds mentioned in the examples both the dihydroxybenzyl and the substituted benzoylamino group mentioned above are, however, attached directly to the piperazine ring nitrogen. No 2,5-dihydroxybenzoylamino compounds, wherein this group would be connected to the piperazine ring through an alkylene chain longer than four carbon atoms, are mentioned specifically in the examples or claims of the published patent application mentioned above.

Antiischaemic 2-pyrimidinylpiperazine derivatives analogous to those described above are disclosed in the published European patent application No. EP 400661A among which derivatives, however, no 2,6-diamino-4--pyrimidinyl compounds are mentioned.

In an other broad class of known compounds containing the above-mentioned three characteristic structural moieties (namely, a hydrocarbon group, a piperazine ring and a 6-membered nitrogen-containing heterocycle) characteristic compounds contain, besides nitrogen heterocycles which are nearly the same as those mentioned in the pre-

ceding paragraph, hydrocarbon groups that are either similar to or different from those mentioned above.

Thus, the characteristic hydrocarbon based moiety is e.g. phenyl, benzyl or benzhydryl group [French patent specification No. 1,507,062; published German patent applications Nos. 1,947,332 and 2,211,738; Belgian patent specification No. 739,283; Canadian patent specification No. 983,497; as well as published Japanese patent application (Kokai) No. 74/76887]; benzodioxolyl or benzodioxanyl group [Canadian patent specifications Nos. 979,894, 983,493, 983,494 and 983,495 as well as published Japanese patent applications Nos. 74/72270, 74/72271, 74/72272 and 74/72273 (Kokai)] as well as 3--trityl-n-propyl group [G.R. Regnier et al.: J. Med. Chem. **15**, 295 (1972)] directly connected to one nitrogen of the piperazine ring. (It is noted that derivatives containing naphthyl group do not occur among these compounds.) A very wide variety of biological effects of a high number of these latter compounds are described, e.g. the vasodilatory, tranquilizing, analgetic, respiration--stimulating effects are discussed. No mention is made about their lipid peroxidation inhibiting action.

In addition to the classes of compounds mentioned above which contain a piperazine ring and other nitrogen--heterocycle(s), e.g. a pyrimidine ring, other compound types are also reported in the literature to possess a lipid peroxidation inhibitory effect. This is exemplified by some compound classes as follows:

Cyclic hydroxamic acids [Y. Teshima et al.: J. Antibiot. **44**, 685 (1991)];

dehydroalanine derivatives [P. Buc-Calceron et al.: Arch. Biochem. Biophys. **273**, 339 (1989)];

acylated polyamines [J. M. Braughler et al.: Biochem. Pharmacol. 37, 3853 (1988)];

glutathione analogues [Drug Data Reports 12, 339 (1990)];

amino analogues of vitamin C (published European patent applications Nos. 446,539 and 447,325);

monocyclic analogues of vitamin E (Japanese patent specification No. 01,226,843);

other derivatives of vitamin E [R. Nikolov: Drug News & Perspectives 5, 507 (1992)];

1,4-benzoquinones [e.g. G. Goto: Chem. Pharm. Bull. 33, 4422 (1985)]; or napthoquinones [Drugs of the Future 14, 692 (1989)];

carboxyalkyl- and hydroxyalkyl-naphthoquinones [K. Okamoto et al.: Chem. Pharm. Bull. 30, 2797 (1982)];

salicylideneamine derivatives [W. Musleh et al.: Neuropharmacology 33, 929 (1994)];

acylamino-7-hydroxyindane derivatives [Y. Oshiro et al.: J. Med. Chem. 34, 2014 (1991)];

methylprednisolone [e.g. H. E. Demopoulos et al.: J. Physiol. Pharm. 60, 1415 (1982)];

flavonoids [e.g. R. Campos et al.: Planta Med. 55, 417 (1989)];

pyrazolinone derivatives [K. Abe et al.: Stroke 19, 480 (1988)];

pyrazolone derivatives (published Japanese patent application No. 62-149,617);

thiazolidinediones [T. Yoshicka et al.: J. Med. Chem. 32, 421 (1989)];

piperidine derivatives [T. Kaneko et al.: Arzneimittelforschung 39, 445 (1989)];

4-arylthiopiperidine derivatives (published European patent application No. 433,167);

dihydropyridinethiones [A.G. Odynets et al.: Eksp. Med. (Riga) **21**, 127 (1986); Chem. Abstr. **106**, 148956];

tetrahydropyridine derivatives [T. Gizur et al.: Eur. J. Med. Chem. **29**, 349 (1994)];

pyrimidinediones (published European patent application No. 447,324);

bis(nicotinoyl-alkylene)-diamines [Drugs of the Future **61**, 586 (1992)];

dihydroquinoline derivatives [A. Blazovics et al.: Free Radical Res. Commun. **4**, 409 (1988)];

quinazoline derivatives (published European patent application No. 302,967);

pyridylquinolines (published European patent application No. 289,365);

pyrimido-pyrimidines [T. Bellido et al.: Meth. Find. Exp. Clin. Pharmacol. **13**, 371 (1991)];

benzothiazines (Japanese patent specification No. 01,287,077);

carbazole derivatives [R. Feuerstein: Pharmacology **48**, 385 (1994)];

anthrone and acridine derivatives [P. Frank: Biochem. Biophys. Res. Commun. **140**, 797 (1986)];

methylated uric acid analogues [Y. Nishida: J. Pharmacol. **43**, 885 (1991)];

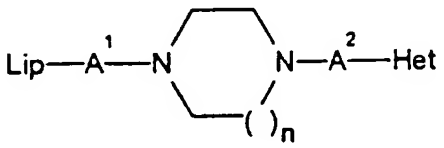
selenium compounds [A. Müller et al.: Biochem. Pharmacol. **33**, 3235 (1984) and A. L. Tappel: Fed. Proc. **24**, 73 (1965)]; and

curcuminoids [S. Toda et al.: J. Ethnopharmacology **23**, 105 (1988)].

The literature data discussed above illustrate, on the one part, that compounds containing a piperazine ring and a mono- or diamino-(N-heterocycle) attached thereto do not necessarily show lipid peroxidation inhibitory activity; and, on the other part, that the presence of the above nitrogen-heterocycles is not inevitable for this activity.

In Example 35 of the Hungarian patent application No. P 92 02172 a compound, namely 1-[6-(2,5-dihydroxybenzoylamino)-caproyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine is described, which is to some degree structurally similar to a variant, containing a benzoyl group, of compounds of formula (I) of the present invention, and exerts a remarkable lipid peroxidation inhibitory effect.

Furthermore, there are known compounds showing certain structural relations to the compounds of formula (I) of the present invention, namely substances of formula (A)



(A)

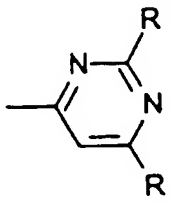
with lipid peroxidation inhibitory effect, which had been disclosed in the published European patent application No. 0574906A, where in formula (A)

Lip means *inter alia* 1- or 2-naphthyloxy; or 1,2,3,4-tetrahydro-6-naphthyloxy substituted by oxo;

A^1 and A^2 represent single bond(s) or C_{1-3} alkylene optionally substituted by hydroxy or oxo;

n is 1 or 2; and

Het stands inter alia for a group of formula (B),



(B)

wherein

R means amino or 1-pyrrolidinyl group.

However, no compounds containing naphthylamino, naphthylthio group or the naphthyl group as a part of an acyl moiety are found among these substances.

The compounds of formula (A) mentioned above showed a remarkable lipid peroxidation inhibitory effect under *in vitro* conditions. Thus, e.g. the compounds containing naphthyloxy or oxo-tetrahydronaphthyloxy group according to Examples 22, 23, 26, 27, 30, 33 and 36 of the published European patent application No. 0574906A inhibited the iron ion-induced lipid peroxidation in rat brain homogenate with an IC_{50} value of lower than 30 μM (the test method will be discussed hereinafter). Under *in vitro* conditions, 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(1-naphthyloxy)propyl]homopiperazine of Example 23 with an IC_{50} value of 9 μM and 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthyloxy)propyl]homopiperazine of Example 27 with an IC_{50} value of 8 μM were found to be the most active compounds. Under *in vivo* conditions in a head injury model in mice a dose of 20 mg/kg of the most active compound among the naphthyloxy derivatives, i.e. the 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthyloxy)propyl]homopiperazine of Example 27, induced a 82 % increase in the total score characterizing the neurologic state of the

animals (the test method will be discussed hereinafter). At the same time, a 30 mg/kg dose of 21-{4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl}-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione [U74006F, see e.g. in: Drugs of the Future **20**, 218 (1995)] resulted in an improvement of 77 % in the same test.

On the other hand it has been found that, in comparison with compounds according to the published European patent application No. 0574906A, some representatives of formula (I) of the present invention showed the same or somewhat stronger *in vitro* lipid peroxidation inhibiting effect, e.g. the IC_{50} value of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]-piperazine of Example 31 was 2 μM; that of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine according to Example 34 was 4 μM; that of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylthio)propyl]homopiperazine according to Example 37 was 10 μM; and that of 1-[6-(2,5-dihydroxybenzoylamino)hexyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine according to Example 1 was 4 μM. In addition, surprisingly, these compounds exerted a much stronger protective action under *in vivo* conditions, and this action can be explained by their lipid peroxidation inhibitory effect detectable under *in vitro* conditions. In other words, these substances showed a surprising surplus effect when they were compared either to known compounds remote from those of formula (I), or to known compounds in some structural relation to those of formula (I), e.g. compounds of formula (A) containing a naphthyloxy group.

Thus, e.g. 1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine (compound of Example 46), in a dose of 1.25 mg/kg which is by an order of magnitude lower than that of the compounds of formula (A) or that of the above-mentioned compound U74006F used as reference substance, resulted in a higher improvement (132 %) of the total score in the above-mentioned *in vivo* head injury test. Similarly, a 2.5 mg/kg dose of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine according to the present invention (compound of Example 34) augmented the total score by 119 % in the same test; and a 2.5 mg/kg dose of 1-[6-(2,5-dihydroxybenzoylamino)hexyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine (compound of Example 1) of the present invention resulted in a total score increase of 125 %. In addition, 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]-piperazine (compound of example 31) according to the present invention proved to be even more active since it augmented the total score by 151 % in a 0.31 mg/kg dose, which is by two orders of magnitude lower than those of the above known compounds.

Summing up, it can be stated that especially high lipid peroxidation inhibitory activity was exerted by those novel synthetic pyrimidine derivatives, wherein said pyrimidine ring bears two identical or different, optionally substituted, amino groups and the carbon atom in position 4 of the pyrimidine ring is attached to one of the nitrogen atoms of a piperazine or homopiperazine ring. Simultaneously, the other nitrogen atom of said piperazine or homopiperazine ring bears a structural subunit containing an optionally substituted naphthyl or

substituted phenyl group as defined in detail hereinbelow.

Thus, the present invention relates to novel pyrimidine derivatives of formula (I) and their salts, wherein R^1, R^2, R^3, X, A and n are as defined above.

Some representative compounds of formula (I) according to the present invention contain one or more asymmetric carbon atom(s); therefore, they can exist either in the form of stereoisomers (e.g. enantiomers or diastereomers) or their mixtures (e.g. racemates of enantiomers). Thus, the scope of the present invention includes also the pure stereoisomers, the racemic and other mixtures of compounds of formula (I) as well as the salts, especially pharmaceutically acceptable salts, of all these compounds.

Hereinbelow, characteristic groups represented by the symbols in formula (I) will be explained.

When R^1 or R^2 in formula (a) being present as R^3 means an optionally substituted amino group, the said substituent of the amino group may be e.g. one or two C_{1-4} alkyl, C_{1-4} alkanoyl, C_{1-4} alkoxycarbonyl optionally substituted by phenyl, C_{1-4} alkylsulfonyl or arylsulfonyl group.

R^1 may be (but not limited to) 1-naphthyl, 2-naphthyl, 1-chloro-2-naphthyl, 4-chloro-1-naphthyl, 5-chloro-2-naphthyl, 1-bromo-2-naphthyl, 5-bromo-2-naphthyl, 6-bromo-2-naphthyl, 1,6-dibromo-2-naphthyl, 5,8-dibromo-2-naphthyl, 2-hydroxy-1-naphthyl, 4-hydroxy-1-naphthyl, 3-hydroxy-2-naphthyl, 1-hydroxy-2-naphthyl, 4-methoxy-1-naphthyl, 6-methoxy-1-naphthyl, 6-methoxy-2-naphthyl, 7-methoxy-2-naphthyl, 4-benzyloxy-1-naphthyl, 1-methylthio-2-naphthyl, 1-methylsulfinyl-2-naphthyl, 1-methylsulfonyl-2-naphthyl, 4-methylthio-1-naphthyl, 4-

-methylsulfinyl-1-naphthyl, 4-methylsulfonyl-1-naphthyl, 4-acetyl-1-naphthyl, 7-acetyl-2-naphthyl, 4-nitro-1--naphthyl, 6-nitro-2-naphthyl, 4-amino-1-naphthyl, 3--amino-2-naphthyl, 6-amino-2-naphthyl, 3-methylamino-1--naphthyl, 3-dimethylamino-1-naphthyl, 3-dimethylamino-2--naphthyl, 3-acetylamino-1-naphthyl, 4-methylamino-1--naphthyl, 4-dimethylamino-1-naphthyl, 6-dimethylamino-2--naphthyl, 4-acetylamino-1-naphthyl, 4-ethoxycarbonylamino-1-naphthyl, 4-benzyloxycarbonylamino-1-naphthyl, 4--methanesulfonylamino-1-naphthyl, 4-(p-toluenesulfonylamino)-1-naphthyl, 3-carboxy-2-naphthyl, 3-methoxycarbonyl-2-naphthyl, 5-carboxamido-2-naphthyl, 7-carboxy--2-naphthyl, 7-methoxycarbonyl-2-naphthyl, 7-carboxamido--2-naphthyl, 3-cyano-2-naphthyl, 5-cyano-2-naphthyl, 6--cyano-2-naphthyl, 1-sulfo-2-naphthyl, 4-sulfo-1-naphthyl, 5,8-disulfo-2-naphthyl, 4-sulfonamido-1-naphthyl, 4-(N,N-diethyl)sulfonamido-1-naphthyl, 4-(N,N-dimethyl)-sulfonamido-1-naphthyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(2-naphthyl)ethyl, 1-naphthoyl, 2-naphthoyl, 2--naphthoylmethyl, 1-hydroxy-2-naphthoyl, 3-hydroxy-2--naphthoyl, 2-hydroxybenzoyl, 2-benzyloxybenzoyl, 2-benzyloxybenzyl, 2,4-dihydroxybenzoyl, 2,5-dihydroxybenzoyl, 2,5-dibenzyloxybenzoyl, 2-(1-naphthyl)acetyl, 2-(2--naphthyl)acetyl group and the like. Within this, when X means a single bond, R^1 preferably represents e.g. 3--hydroxy-2-naphthyl or 1-hydroxy-2-naphthyl group; whereas in the case, when the meaning of X is different from a single bond, R^1 preferably stands for 1-naphthyl, 2-naphthyl, 2-naphthylmethyl, 2-(2-naphthyl)acetyl group or 2,5-dihydroxybenzoyl.

It can be seen from the above list that a substituent optionally being present on the naphthyl group may be at-

tached to any carbon atom of any ring of the naphthyl moiety; but preferably, it is attached to a carbon atom of the same ring, which bears the X group.

Certain R^4 and R^5 substituents within the groups of formula (a) being present as R^1 (e.g. hydroxyl, amino and/or carboxyl group) may be protected, if desired. Thus, in the above definitions, e.g. a C_{1-4} alkoxy group or a C_{1-4} alkoxy group substituted by a phenyl group can be considered as a protected hydroxyl group. Similarly, an amino group substituted by a C_{1-4} alkanoyl or C_{1-4} alkoxycarbonyl group optionally substituted by a phenyl group, or C_{1-4} alkylsulfonyl or arylsulfonyl group may be considered to be a protected amino group. Furthermore, a C_{1-4} alkoxycarbonyl moiety may represent a protected carboxyl group, too.

R^2 and R^3 may be (but not limited thereto), independently from each other, amino, 1-pyrrolidinyl, 1-piperidinyl, hexahydro-1H-azepin-1-yl or octahydroazocin-1-yl group and preferably amino and/or pyrrolidinyl group.

X may stand (but not limited thereto) e.g. for a single bond, sulfur optionally substituted by one or more oxygen atom(s), an unsubstituted nitrogen or nitrogen optionally substituted by methyl, ethyl, formyl, acetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, methanesulfonyl or p-toluenesulfonyl group and preferably a simple chemical bond, sulfur or unsubstituted nitrogen.

The meaning of A may be e.g. (but not limited thereto) methylene, 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 1,7-heptylene, 1,8-octylene; carbonyl; 1-oxo-1,2-ethylene, 1-oxo-2-methyl-1,2-ethylene, 1-oxo-1,3-propylene, 2-oxo-1,3-propylene, 1-oxo-2-amino-1,3-propylene; 1-oxo-2-(tert-butoxy-

carbonylamino)-1,3-propylene; 2-hydroxy-1,3-propylene, 2--acetoxy-1,3-propylene, 2-methoxy-1,3-propylene, 2-benzyloxy-1,3-propylene; 1-oxo-2-bromo-1,3-propylene, 2--chloro-1,3-propylene, 2-amino-1,3-propylene, 2-methylamino-1,3-propylene, 2-dimethylamino-1,3-propylene; 2--acetylamino-1,3-propylene, 2-(benzyloxycarbonylamino)--1,3-propylene or 2-methanesulfonylamino-1,3-propylene group and the like; and preferably, e.g. 1,2-ethylene, 1,3-propylene, 1,6-hexylene, carbonyl, 1-oxo-1,2-ethylene or 2-hydroxy-1,3-propylene group.

Similarly to what was described for the substituents of the group R^1, among the substituents of the alkylene chain being present as A, a C_{1-4} alkoxy group optionally substituted by a phenyl group can be considered as a protected hydroxyl group; whereas e.g. an amino group substituted by a C_{1-4} alkanoyl group or a C_{1-4} alkoxycarbonyl group optionally substituted by a phenyl group or C_{1-4} alkylsulfonyl group may be considered to be a protected amino group.

In the formula (I) the value of n is 1 or 2, and preferably 1.

Suitable salts of the compounds of formula (I) containing basic groups are e.g. the salts formed with inorganic acids (e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acid and the like) or with organic acids (e.g. acetic, tartaric, citric, fumaric, succinic, maleic, methanesulfonic, ethanesulfonic or p-toluenesulfonic acid and the like). Furthermore, compounds of formula (I) containing a phenyl or naphthyl group substituted by hydroxy and/or carboxy can form salts with bases in addition to the acid-addition salts. Suitable salts formed with bases are e.g. the alkali metal salts (such as sodium or potas-

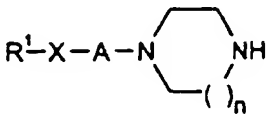
sium salts), alkaline earth metal salts (e.g. calcium or magnesium salts) and the like; as well as salts formed with some organic bases such as ethanolamine, diethanolamine, ethylenediamine and the like.

As an other aspect of the invention, there is provided a process for the preparation of the compounds of formula (I) and their salts, the variants a) to g) of which are illustrated in the reaction schemes A to G. Thus, according to the process of the invention

a) in order to obtain compounds of formula (I), wherein R^1, R^2, R^3, X and n are as defined above; and

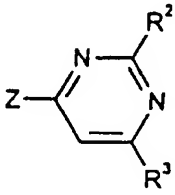
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino,

a compound of formula (II),



(II)

wherein R^1, X, A and n are as defined above, is reacted with a compound of formula (III),



(III)

wherein R^2 and R^3 are as defined above and Z means a leaving group; or

b) in order to obtain compounds of formula (I), wherein R^1, R^2, R^3 and n are as defined above;

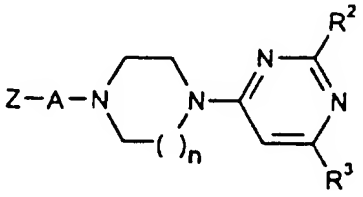
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino; and

X is as defined for the formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atom(s),

a compound of formula (IV),

$$R^1\text{-}XH \qquad (IV)$$

wherein R^1 and X are as defined above, is reacted with a compound of formula (V),



(V)

wherein R^2, R^3, A and n are as defined above and Z means a leaving group; or

c) in order to obtain compounds of formula (I), wherein R^1, R^2, R^3 and n are as defined above;

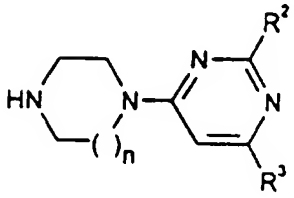
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino; and

X is as defined above, with the proviso that it may not be a single bond,

a compound of formula (VI),

$$R^1\text{-}X\text{-}A\text{-}Z \qquad (VI)$$

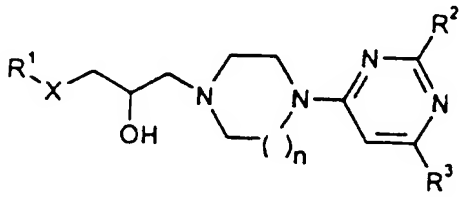
wherein R^1, X and A are as defined above and Z means a leaving group, is reacted with a compound of formula (VII),



(VII)

wherein R^2, R^3 and n are as defined above; or

d) in order to obtain compounds of formula (Ia)



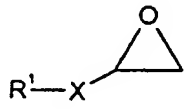
(Ia)

representing a narrower scope of compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above; and

X is as defined above, with the proviso that it may not be a single bond,

a compound of formula (VIII),



(VIII)

wherein R^1 and X are as defined above, is reacted with a compound of formula (VII), wherein

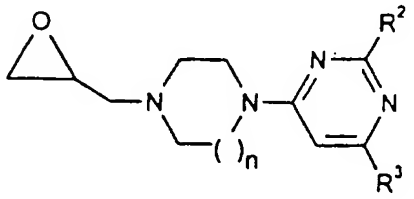
R^2, R^3 and n are as defined above; or

e) in order to obtain compounds of formula (Ia) representing a narrower scope of the compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above; and

X is as defined for formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atom(s),

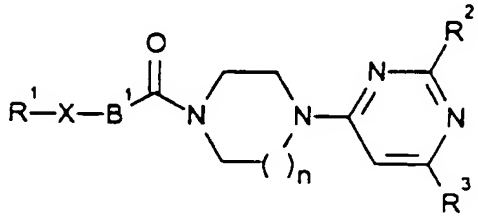
a compound of formula (IV), wherein R^1 and X are as defined above, is reacted with a compound of formula (IX),



(IX)

wherein R^2, R^3 and n are as defined above; or

f) in order to obtain compounds of formula (Ib)



(Ib)

representing a narrower scope of compounds of formula (I), wherein

R^1, R^2, R^3, X and n are as defined above; and

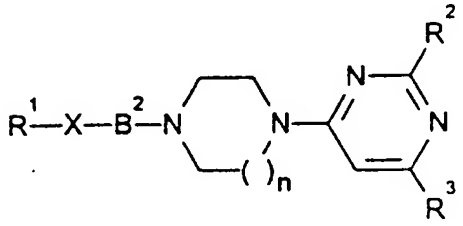
B^1 means a single bond or a straight or branched chain C_{1-4} alkylene group optionally substituted by halogen, C_{1-4} alkoxy, C_{1-4} alkanoyloxy and/or an optionally substituted amino group,

a carboxylic acid of formula (X),

$$R^1\text{-}X\text{-}B^1\text{-}COOH \qquad (X)$$

wherein R^1, X and B^1 are as defined above, or a reactive derivative thereof activated at the carboxyl group is reacted with a compound of formula (VII), wherein R^2, R^3 and n are as defined above; or

g) in order to obtain compounds of formula (Ic)



(Ic)

representing a narrower scope of the compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above;

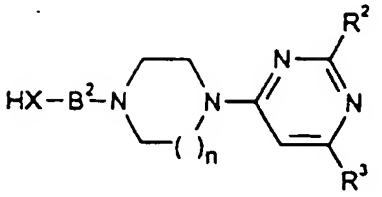
X stands for a nitrogen atom optionally substituted by a C_{1-4} alkyl group; and

B^1 means a straight or branched chain C_{2-8} alkylene group optionally substituted by hydroxy, C_{1-4} alkoxy and/or di(C_{1-4} alkyl)amino group,

a compound of formula (XI),

$$R^1\text{-}Z \qquad (XI)$$

wherein Z means a leaving or hydroxyl group and R^1 is as defined above, with the proviso that p, q and r are 0 when Z means a hydroxyl group, is reacted with a compound of formula (XII),



(XII)

wherein R^1, R^3, B^2, X and n are as defined above,

and, if desired, a compound of formula (I) obtained by using any of the process variants a) to g) is transformed to an other compound of formula (I) in a manner known *per se*; and/or a protective group optionally being present is removed; and/or, if desired, a base is prepared from an obtained salt of the compound of formula (I); or the obtained base is transformed to one of its salts, e.g. to its acid-addition salt.

Pure enantiomers of a compound of formula (I) containing one single centre of asymmetry can be obtained e.g. by resolution of a racemic compound of formula (I) prepared by means of racemic reagents by using methods known *per se* (e.g. by formation and separation of diastereomeric salts or other derivatives); or, by carrying out the above process variants with the pure enantiomeric forms of the required reagents.

The diastereomers of a substance of formula (I) including more centres of asymmetry can be separated by using methods known *per se*, e.g. chromatography, fractional crystallization or other similar methods.

It is obvious to those skilled in the art that when some substituents of the starting compounds, e.g. the R^1 and/or A group contain reactive groups (e.g. hydroxy, amino, carboxy or the like) not to be transformed in the respective reaction, these groups can be protected by

methods generally known in organic chemistry. Then, after the desired transformation, the protective group(s) is (are) removed without any undesired change in other parts of the molecule. For protection of the groups mentioned, usual protective groups known *per se* may be employed, e.g. C_{1-4} alkyl groups optionally substituted by an aryl group (such as tert-butyl or benzyl group) for protecting hydroxyl groups; C_{1-4} alkoxycarbonyl groups optionally substituted by an aryl, e.g. phenyl group (e.g. tert-butoxycarbonyl or benzyloxycarbonyl group), C_{1-4} alkanoyl groups (e.g. formyl or acetyl group), C_{1-4} alkanesulfonyl groups (e.g. methanesulfonyl group) or p-toluenesulfonyl group for protecting amino groups; and e.g. C_{1-4} alkyl (e.g. ethyl) ester groups for protecting carboxyl groups.

In addition to the protective groups exemplified above any other protective group known *per se* [such as the ones discussed by T. W. Greene and P. Wuts in: "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, N.Y. (1991)] may be employed. Suitable methods of cleaving protective groups are discussed in the same work cited above.

It is noted that certain reaction steps of the process according to the present invention can be performed also without the transient protection of reactive groups not participating in the desired reaction.

The preferred embodiments of variants of the process according to the invention are hereinbelow discussed in detail.

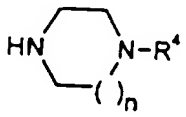
Process variant a)

(Reaction scheme A)

A compound of formula (II) is reacted with a compound of formula (III) in a suitable solvent such as chlorobenzene, dimethylformamide, dimethylacetamide, N-methylpyrrolidone or the like; or optionally without any solvent, at a temperature between 100 °C and 200 °C and, if necessary, in the presence of a base, e.g. inorganic base such as potassium carbonate or sodium hydroxide, or an organic base, e.g. triethylamine or pyridine as acid-binding agent. When carrying out the reaction in the absence of any base, the liberated acid of formula H-Z may be bound by the product of formula (I).

The intermediates of formula (II) used in the present process variant are new and as such they also fall within the scope of the present invention. These compounds can be prepared in various routes depending on the meaning of X and A as illustrated in reaction schemes H and I.

A common characteristic feature of these methods consists in a common starting compound of formula (XIII),



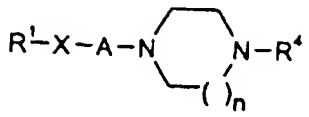
(XIII)

wherein

n is the same as defined for formula (I); and

R^1 means an amine-protecting group,

which is transformed to a compound of formula (XIV),



(XIV)

wherein

R^1, X, A and n are as defined for formula (I); and

R^4 stands for an amine-protecting group,

by using any of methods A) to E) to be discussed hereinafter; then, after cleaving the protective group, a compound of formula (II) is obtained. The difference between the methods starting from compounds of formula (XIII) is that they provide the intermediate of formula (XIV) by means of various reagents. The variants of preparing the intermediates of formula (XIV) are described hereinafter in detail [methods A) to C) are illustrated by reaction scheme H, whereas methods D) and E) are shown by reaction scheme I].

Method A)

In order to obtain a compound of formula (II), wherein

R^1 and n are as defined for formula (I);

X means a sulfur atom optionally substituted by one or two oxygen atom(s) or an optionally substituted nitrogen atom; and

A stands for C_{1-3} alkylene substituted by hydroxy, C_{1-4} alkoxy or C_{1-4} alkanoyloxy or optionally substituted by oxo at the carbon atom attached to X;

a compound of formula (XIII), wherein R^4 means an amine-protecting group and n is as defined above, may be reacted with a compound of formula (VI), wherein R^1, X and

A are as defined above, and Z is a leaving group, to give a compound of formula (XIV), wherein R^1, R^2, X, A and n are as defined above.

This reaction is suitably carried out in a solvent, e.g. ethanol, propanol, acetonitrile or the like, in the presence e.g. of an inorganic base such as potassium carbonate or sodium hydroxide, in a temperature range between 20 °C and 100 °C.

In the starting compounds of formula (XIII), R^4 means an amine-protective group, e.g. alkanoyl group such as formyl group or preferably a C_{1-4} alkoxycarbonyl group optionally substituted by aryl group such as tert-butoxycarbonyl or benzyloxycarbonyl group. A part of the protected piperazine and homopiperazine derivatives of formula (XIII) is known [see e.g. T. R. Herrin et al.: J. Med. Chem. **18**, 1216 (1975)] or can be prepared by methods analogous to known ones.

In the compounds of formula (VI) used as starting materials in method A), Z means a leaving group, suitably e.g. halogen such as chlorine, bromine or iodine; or an aliphatic or aromatic sulfonyloxy group such as methanesulfonyloxy or p-toluenesulfonyloxy group. A part of the compounds of formula (VI) is known [see e.g. E.K. Harwill et al.: J. Org. Chem. **17**, 1957 (1952); and L.M. Werbel: J. Med. Chem. **6**, 637 (1963)] or they can be prepared by using simple methods known *per se*. Thus, compounds of formula (VI) containing C_{2-5} alkylene group as A may be prepared e.g. as illustrated in reaction scheme J starting with alcohols of formula (XIX),

$$R^1\text{-}X\text{-}B^2\text{-}OH \qquad (XIX)$$

wherein

R^1 and X are as defined above; and

B^2 stands for a C_{2-4} alkylene group

by using methods known *per se*.

On the other hand, compounds of formula (VI), containing an alkylene group substituted by oxo at the carbon atom attached to X, are suitably prepared by reacting an appropriate compound of formula (IV), wherein R^1 and X are as defined above, with a carboxylic acid of formula (XX),

$$HOOC-B^3-Z \qquad (XX)$$

wherein

B^3 means a C_{1-3} alkylene group and

Z is a leaving group,

or with a reactive derivative thereof activated at the carboxyl group (see reaction scheme J).

The compounds of formulae (XIX) and (XX) are known from the literature [see e.g. J.S. Pierce and R. Adams: J. Am. Chem. Soc. **45**, 790 (1923); and R. E. Foster et al.: J. Am. Chem. Soc. **68**, 1328 (1946)] or partly they are commercially available.

Method B)

In order to obtain compounds of formula (II), wherein R^1 and n are as defined for formula (I);

X means a sulfur atom optionally substituted by one or two oxygen atom(s) or an optionally substituted nitrogen atom; and

A stands for 2-hydroxy-1,3-propylene group,

a protected compound of formula (XIII), wherein

R^4 stands for an amine-protective group; and

n is as defined above,

is reacted with an epoxide of formula (VIII), wherein R^1 and X are as defined above, to obtain a compound of formula (XIV), wherein R^1, R^4, X, A and n are as defined above.

This reaction is conveniently performed in a solvent such as an alcohol, e.g. ethanol, at a temperature between 20 °C and 100 °C, preferably at the boiling point of the solvent.

A part of the starting compounds of formula (VIII) is known [see e.g. British patent specification No. 1,592,524; Soviet patent specification No. 1,286,596; as well as the published Japanese patent application No. 79-01300] or can be prepared by using methods analogous to known ones such as methods illustrated hereinafter by examples.

Method C)

Alternatively, in order to obtain compounds of formula (II), wherein

R^1, X and n are as defined for formula (I); and

A stands for C_{1-4} alkylene substituted by oxo at the carbon atom attached to the nitrogen-containing heterocycle,

a protected compound of formula (XIII), wherein

R^4 means an amine-protecting group; and

n is as defined above,

is reacted with a carboxylic acid of formula (X), wherein R^1 and X are as defined above; and

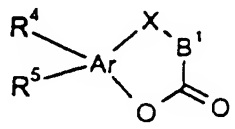
B^1 means a single bond or C_{1-3} alkylene,

or a reactive derivative thereof activated at the carboxyl group to obtain a compound of formula (XIV), wherein R^2, R^4, X, A and n are as defined above.

Compounds of formula (XIII) can be reacted with the free acid form of compounds of formula (X). In such cases, the reaction can be carried out in an inert solvent, e.g. dimethylformamide, methylene chloride, ethanol or the like, in the presence of a condensing agent, e.g. N,N'-dicyclohexylcarbodiimide or carbonyldiimidazole, optionally by using an additive agent, e.g. 1-hydroxybenzotriazole. However, it is suitable to use the compounds of formula (X) in the form of their reactive derivatives activated at the carboxyl group and not in their free acid form. Such reactive forms are e.g.: acyl halides, e.g. an acyl chloride or acyl bromide; active esters, e.g. an aryl ester such as a phenyl ester; symmetric or mixed anhydrides, e.g. a mixed anhydride prepared by means of a chloroformate ester and the like. Carboxylic acids of formula (X), wherein

R^2 is as defined for formula (I), with the proviso that in formula (a) at least one of R^4 and R^5 stands for hydroxy, and each of p, q and r are 0,

can be used also in their lactone forms of formula (XXI),



(XXI)

wherein

X and B^1 are as defined for formula (X); and

Ar, R^4 and R^5 are as defined for Ar, R^4 and R^5, respectively, forming a part of the group of formula (a), with the proviso that R^4 and R^5 may not mean unsubstituted amino or amino substituted by a C_{1-4} alkyl group.

These lactons are the intramolecular aryl esters of the respective acids.

Some compounds of formula (X) such as 1-naphthoic acid, 2-naphthoic acid, 1-naphthylacetic acid, 1-hydroxy--2-naphthoic acid, 3-hydroxy-2-naphthoic acid are commercially available; whereas other ones, e.g. 2-(2-hydroxy--1-naphthyl)acetic acid, 2-(3-hydroxy-2-naphthyl)acetic acid or 3-(2-hydroxy-1-naphthyl)propionic acid and their lactones of formula (XXI) [see e.g. Y. Ogata et al.: J. Org. Chem. **16**, 1588 (1951); A.F. Hardman: J. Am. Chem. Soc. **70**, 2119 (1948); as well as H. Krzikalla and B. Eistert: J. prakt. Chem. **143**, 50 (1935)], furthermore 2-(2--naphthylthio)acetic acid and 2-(2-naphthylamino)acetic acid [see e.g. T. M. Furman et al.: J. Am. Chem. Soc. **82**, 1450 (1960); and C. A. Bischoff and A. Hausdörfer: Chem. Ber. **23**, 2005 (1980)] are known compounds. Other substances of formula (X) may be prepared by using methods analogous to the above ones.

Method D)

In order to obtain compounds of formula (II), wherein R^4 and n are as defined for formula (I);

X is as defined for formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atom(s); and

A stands for C_{1-4} alkylene substituted by hydroxy, C_{1-4} alkoxy, C_{1-4} alkanoyloxy or optionally substituted by oxo at the carbon atom attached to X,

a compound of formula (XIII), wherein

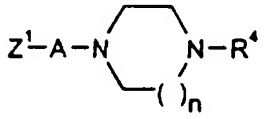
R^4 means an amine-protective group; and

n is as defined above,

is first reacted with a compound of formula Z^1-A-Z^2, wherein

A is as defined above; and

Z^1 as well as Z^2 mean, independently from each other, leaving groups, to give a compound of formula (XV),



(XV)

wherein

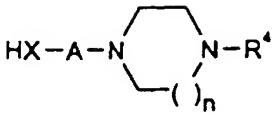
R^4, A, Z^1 and n are as defined above.

When this latter substance is reacted with a compound of formula (IV), wherein R^1 and X are as defined above, a compound of formula (XIV) is obtained, wherein R^1, R^4, X, A and n are as defined above.

Both reactions may be carried out similarly as described in method A).

The starting compounds of formula Z^1-A-Z^2 are commercially available or may be prepared by using simple methods known *per se*.

On the other hand, on substituting amino or C_{1-4} alkylamino for the leaving group Z^1 in a compound of formula (XV) in a way known *per se*, a substance of formula (XVI),



(XVI)

wherein

R^4, A and n are as defined above; and

X represents a nitrogen atom optionally substituted by a C_{1-4} alkyl group,

is obtained. This substitution reaction can be performed e.g. by reacting the compound of formula (XV) with ammonia, a C_{1-4} alkylamine or potassium phthalimide in a manner known *per se* in an inert solvent, such as an aliphatic alcohol, dimethylformamide or the like. On using potassium phthalimide, the phthalimido compound obtained is treated e.g. with hydrazine in an aliphatic alcohol in a manner known *per se* to provide the required substance of formula (XVI).

By reacting a compound of formula (XVI) with a compound of formula (XI), wherein

R^1 is as defined above; and

Z means hydroxy or a leaving group,

similarly as discussed e.g. in process variant g) to be described hereinafter, again a compound of formula (XVI), wherein

R^1, R^4, A and n are as defined above; and

X stands for a nitrogen atom optionally substituted by a C_{1-4} alkyl group,

is obtained.

Method E)

Alternatively, in order to prepare compounds of formula (II), wherein

R^1 and n are as defined for formula (I);

X is as defined for formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atoms; and

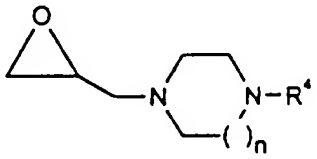
A stands for 2-hydroxy-1,3-propylene group,

a protected compound of formula (XIII), wherein

R^4 means an amine-protective group; and

n is as defined above,

is first reacted with epichlorohydrin and then the obtained epoxide of formula (XVII),



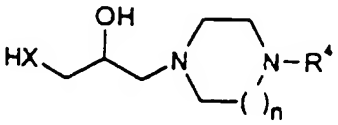
(XVII)

wherein R^1 and n are as defined above, is reacted with a compound of formula (IV), wherein R^1 and X are as defined above to give a compound of formula (XIV), wherein R^1, R^4, X, A and n are as defined above.

A compound of formula (XIII) can be reacted with epichlorohydrin e.g. by using methods described above for the preparation of the compounds of formula (VIII). On the other hand, compounds of formula (XVII) obtained as intermediates can be reacted with compounds of formula (IV) under conditions discussed in method B) above.

According to an other variant of process E) an epoxide of formula (XVII) prepared as described above is reacted with ammonia or a C_{1-4} alkylamine in a suitable sol-

vent, e.g. water or an aliphatic alcohol or a mixture thereof, to give a compound of formula (XVIII),



(XVIII)

wherein

R^4 and n are as defined above; and

X means a nitrogen atom optionally substituted by a C_{1-4} alkyl group,

then the obtained compound is reacted with a compound of formula (XI), wherein

R^3 is as defined above; and

Z stands for a leaving group,

under the conditions discussed in method D), again to obtain a compound of formula (XIV), wherein

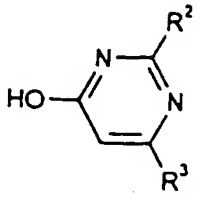
R^3, R^4, A and n are as defined above; and

X stands for a nitrogen atom optionally substituted by a C_{1-4} alkyl group.

The protective group R^4 can be removed from compounds of formula (XIV) prepared by the above methods A) to E) to afford compounds of formula (II). Thus, alkanoyl type protective groups can be removed by acidic or alkaline treatment; C_{1-4} alkoxycarbonyl groups can be removed e.g. by treatment with an acid; whereas C_{1-4} alkoxycarbonyl groups substituted by an aryl group can be split off e.g. by catalytic hydrogenation.

A part of the starting compounds of formula (III) used in process variant a) is known [see e.g. B. Roth et al.: J. Am. Chem. Soc. 72, 1914 (1950); and published PCT

patent application No. WO 87/01706], whereas another part thereof can be obtained from starting compounds of formula (XXII),



(XXII)

wherein R^2 and R^3 are as defined for formula (I), by using methods known *per se* in a route illustrated by the reaction scheme K.

By using process variant a), e.g. the following characteristic compounds according to the present invention can be prepared:

1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[2-dimethylamino-3-(2-naphthylthio)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-{2-hydroxy-3-[N-methyl-N-(2-naphthyl)amino]propyl}piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[N-(2-naphthyl)-carbamoylmethyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[2-(2-naphthylthio)-acetyl]piperazine and

1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-hydroxy-1-naphthyl)propionyl]piperazine.

Process variant b)

(Reaction scheme B)

A compound of formula (IV) is reacted with a compound of formula (V) in a suitable solvent, e.g. ethanol, acetone or dimethylformamide, conveniently in the presence of a base such as an inorganic base, e.g. potassium carbonate or sodium hydroxide, or an organic base, e.g. pyridine or triethylamine, at a temperature between room temperature and the boiling point of the solvent used.

The starting compounds of formula (IV) are commercially available whereas the compounds of formula (V) are partly known (see e.g. the published European patent application No. 0,574,906A); or they can be prepared similarly to known substances by using known methods.

By using process variant b), e.g. the following characteristic compounds according to the present invention can be prepared:

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylamino)acetyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(4-nitro-1-naphthylamino)acetyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylthio)acetyl]piperazine, and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylthio)acetyl]homopiperazine.

Process variant c)

(Reaction scheme C)

A compound of formula (VI) is reacted with a compound of formula (VII) in an inert solvent, e.g. acetone, acetonitrile, or dimethylformamide, suitably in the presence of a base, e.g. potassium carbonate or the like, at a temperature between room temperature and the boiling point of the solvent used.

The preparation of compounds of formula (VI) has been described above; see method A) for the preparation of the intermediates of formula (II) used in process variant a).

A part of compounds of formula (VII) is known (see e.g. the published PCT patent application No. 87/01706) whereas an other part thereof can be prepared analogously to known compounds by using methods known *per se*.

By using process variant c), e.g. the following characteristic compounds according to the present invention can be prepared:

1-{6-[N-(2,5-dibenzyloxybenzoyl)amino]hexyl}-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(2-naphthyl)carbamoylmethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(1-sulfo-2-naphthyl)carbamoylmethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(2-methyl-1-naphthyl)carbamoylmethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(7-ethoxycarbonyl-1-naphthyl)carbamoylmethyl]-piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(7-acetyl-2-naphthyl)carbamoylmethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(4-dimethylaminosulfonyl-1-naphthyl)carbamoyl-methyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(4-methylthio-1-naphthyl)carbamoylmethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(4-methylsulfonyl-1-naphthyl)carbamoylmethyl]-piperazine and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-naphthylamino)propyl]piperazine.

Process variant d)

(Reaction scheme D)

A compound of formula (VIII) is reacted with a compound of formula (VII) in an inert solvent, e.g. a halogenated hydrocarbon such as methylene chloride or in an alcohol, e.g. ethanol or the like, at a temperature between room temperature and the boiling point of the solvent used.

Concerning the preparation of compounds of formula (VIII) see the above description for the preparation of the starting compounds for process variant a).

By using process variant d), e.g. the following characteristic compounds according to the present invention can be prepared:

1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(1-naphthylamino)propyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(1-naphthylamino)propyl]piperazine,

(±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

(-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

(+)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-hydroxy-3-[N-methanesulfonyl-N-(2-naphthyl)amino]propyl}-piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-hydroxy-3-[N-methyl-N-(2-naphthyl)amino]propyl}-piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(1-naphthylamino)propyl]homopiperazine,

(±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine,

(-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine,

(+)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine,

1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-[6-amino-2-(1-piperidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine,

1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine

and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy--3-(2-naphthylthio)propyl]homopiperazine.

Process variant e)

(Reaction scheme E)

A compound of formula (IV) is reacted with a compound of formula (IX) under conditions described for process variant d).

The starting compounds of formula (IX) can simply be prepared by reacting the compounds of formula (VII) with epichlorohydrin in a manner described e.g. for the preparation of compounds of formula (VIII) as illustrated by reaction scheme L.

By using the present process variant e), e.g. the following characteristic compounds according to the invention can be prepared:

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy--3-(2-naphthylthio)propyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy--3-(2-naphthylamino)propyl]piperazine,

and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy--3-(2-naphthoylmethylamino)propyl]piperazine.

Process variant f)

(Reaction scheme F)

The free acid form of a compound of formula (X) or a reactive form thereof activated at the carboxyl group is reacted with a compound of formula (VII). This reaction can be carried out under similar conditions as the starting compounds of formula (II) of process variant a) are obtained according to the above-described method C).

By using the present process variant f), e.g. the following characteristic compounds according to the present invention can be prepared:

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-naphthoyl)homopiperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)homopiperazine,

1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine,

1-[6-amino-2-(1-piperidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3-hydroxy-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3-hydroxy-2-naphthoyl)homopiperazine,

1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3-hydroxy-2-naphthoyl)piperazine,

1-[6-amino-2-(1-piperidinyl)-4-pyrimidinyl]-4-(3-hydroxy-2-naphthoyl)piperazine,

1-[6-amino-2-(hexahydro-1H-azepin-1-yl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine,

(-)-1-(2,6-diamino-4-pyrimidinyl)-4-[2-(6-methoxy-2-naphthyl)propionyl]piperazine,

(-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(6-methoxy-2-naphthyl)propionyl]piperazine,

(-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(6-methoxy-2-naphthyl)propionyl]homopiperazine,

(±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N--(tert-butoxycarbonyl)-3-(1-naphthyl)alanyl]piperazine,

(±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N--(tert-butoxycarbonyl)-3-(2-naphthyl)alanyl]piperazine,

(-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N--(tert-butoxycarbonyl)tyrosyl]piperazine,

(+)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N--(tert-butoxycarbonyl)phenylalanyl]piperazine,

1-(5-bromo-2-naphthoyl)-4-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]piperazine,

1-(5,8-dibromo-2-naphthoyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2--hydroxy-1-naphthyl)propionyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2--hydroxy-1-naphthyl)acetyl]piperazine,

1-[6-amino-2-(1-piperidinyl)-4-pyrimidinyl]-4-[3-(2--hydroxy-1-naphthyl)propionyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3--methylamino-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3--dimethylamino-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3--acetylamino-2-naphthoyl)piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(3--trifluoroacetylamino-2-naphthoyl)piperazine,

1-(5-cyano-2-naphthoyl)-4-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]piperazine,

1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-hydroxy-1-naphthyl)propionyl]piperazine,

and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(3-hydroxy-2-naphthyl)acetyl]piperazine.

Process variant g)

(Reaction scheme G)

A compound of formula (XI) containing a hydroxyl group as Z is reacted with a compound of formula (XII) suitably in an appropriate solvent, e.g. water, an alcohol such as ethanol or in a polar, aprotic solvent such as dimethylformamide, dimethylacetamide and the like, or in the mixture thereof, at the boiling point of the solvent or without any solvent, at a temperature between 120 °C and 250 °C, optionally in the presence of a suitable catalyst, e.g. sodium hydrogen sulfite or the like, optionally in a closed vessel under pressure.

A compound of formula (XI) containing a leaving group as Z can be reacted with a compound of formula (XII) e.g. under conditions discussed under process variant c).

A part of the starting compounds of formula (XI) is commercially available; others can be prepared by using methods known from the literature [see e.g. K. Fries: Ber. **58**, 2848 (1925)].

The compounds of formula (XII) can be prepared e.g. by using methods illustrated in the reaction scheme M. Thus, a compound of formula (VII), wherein R^2, R^3 and n are as defined for formula (I), can be reacted with a compound of formula (XXIII),

$$R^6\text{-}X\text{-}B^2\text{-}Z \qquad \text{(XXIII)}$$

wherein

B^2 stands for a straight or branched chain C_{1-4} alkylene group optionally substituted by hydroxy, C_{1-4} alkoxy and/or di(C_{1-4} alkyl)amino;

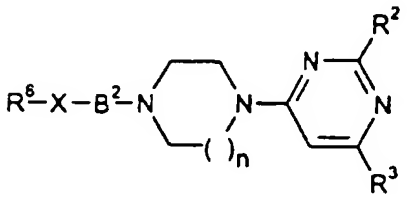
Z means a leaving group;

R^6 is an amine-protective group; and

X means a nitrogen atom optionally substituted by a C_{1-4} alkyl group; or

R^6 and X together stand for a nitrogen atom protected by a bivalent amine-protective group, e.g. phthalimido group;

e.g. under conditions similar to those described in process variant c), then the amine-protective group is removed from the obtained compound of formula (XXIV)



(XXIV)

in a known manner, e.g. by hydrogenolysis, hydrolysis or hydrazinolysis.

Alternatively, for preparing compounds of general formula (XII) containing a 2-hydroxy-1,3-propylene group as B^2, a compound of formula (VII) mentioned above, wherein R^2, R^3 and n are as defined for formula (I), is reacted with epichlorohydrin as described above under process variant e) and illustrated by reaction scheme L, to give an epoxide of formula (IX), wherein R^2, R^3 and n are as defined for formula (I), then the obtained compound of formula (IX) is reacted with ammonia or with a

reagent capable to introduce an amino group (such as hexamethylenetetramine or the like) or with a C_{1-4} alkylamine.

By using the present process variant g), e.g. the following characteristic compounds according to the present invention can be prepared:

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylamino)ethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-[2-(2-naphthoylamino)ethyl]piperazine and

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-[2-(2-naphthyl)acetylamino]ethyl}piperazine.

When desired, a compound of formula (I) prepared by employing one of the process variants a) to g) described above can be transformed to other compounds of formula (I) by using methods known *per se*. Thus, e.g. an aromatic ring being present in group R^1 can be halogenated by a suitable halogenating agent, e.g. elementary halogen (such as chlorine or bromine) or an other convenient reagent (such as an N-halosuccinimide or sulfuryl halide); or nitrated by an appropriate nitrating agent, e.g. concentrated nitric acid or a mixture of an alkali metal nitrate and a strong acid (e.g. sulfuric or trifluoroacetic acid).

Any nitro group occurring as a substituent of the group R^1 may be reduced to an amino group by means of a suitable reducing agent, e.g. elementary hydrogen in the presence of a noble metal catalyst or by using a complex hydride, e.g. sodium borohydride.

Any carbonyl group optionally being present in the aliphatic moiety of the group R^1 may be reduced to methylene group by means of a suitable reducing agent, such

as a complex metal hydride, e.g. lithium aluminum hydride optionally in the presence of a Lewis acid, e.g. aluminum trichloride.

Any sulfur atom in the alkylthio group being present as a substituent of the group R^1 or occurring as X can be oxidized by suitably choosing the amount of an appropriate oxidizing agent, e.g. m-chloroperbenzoic acid, to transform the sulfur atom being present at said site to a sulfur atom substituted by one or two oxygen atom(s).

Any carboxyl group occurring as a substituent of the group R^1 may be esterified with an alcohol, e.g. an aliphatic alcohol, suitably in the presence of an inorganic or organic acid (such as hydrochloric, sulfuric, p--toluenesulfonic acid and the like) as catalyst. Conversely, an esterified carboxyl group being present as a substituent of the group R^1 can be hydrolyzed to the free acid by using an aqueous solution of a base (e.g. an alkali metal hydroxide or carbonate); or it can be reacted with ammonia or an aliphatic amine to obtain the respective carboxamide. A nitrogen-unsubstituted carboxamide can be transformed to the corresponding cyano compound by treatment with a suitable dehydrating agent (e.g. sulfuric acid, phosphorus pentoxide, polyphosphoric acid or the like). Furthermore, a cyano group can be hydrolyzed with a strong acid (such as hydrochloric, sulfuric or phosphoric acid and the like) or a base (such as sodium hydroxide, potassium carbonate and the like) to a carboxamido or carboxyl group depending on the reaction conditions.

Any NH or OH group occurring as a substituent of the R^1 and/or A group can be acylated to an N-acyl or O-acyl derivative, respectively, by means of an appropriate acy-

lating agent (e.g. acyl chloride, acid anhydride, active ester, mixed anhydride or the like); or can be transformed to an N-alkyl or O-alkyl derivative, respectively, by means of a usual alkylating agent (such as an alkyl halide, alkyl sulfate, aromatic sulfonate ester or the like).

Finally, a hydroxyl group can be replaced by a halogen atom by means of a convenient halogenating agent (such as thionyl chloride, phosphorus pentachloride, phosphorus pentabromide or the like) and subsequently, this halogen can be replaced by an amino or alkoxy group by using the respective amine or alkoxide.

The following characteristic compounds according to the present invention can be obtained by methods given as examples for the above additional transformations:

(±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(1-naphthyl)alanyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylmethylamino)ethyl]piperazine,

1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-[2-(2-naphthyl)ethylamino]ethyl}piperazine and

1-[2-acetoxy-3-(N-acetyl-2-naphthylamino)propyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine.

The compounds of formula (I) according to the present invention and their pharmaceutically acceptable salts possess valuable biological effects. More particularly, these compounds inhibit the peroxidation of lipids and therefore, they are useful to treat diseases and pathological conditions where the inhibition of lipid peroxidation is desirable.

The lipid peroxidation inhibiting effect of the compounds according to the present invention and their phar-

maceutically acceptable salts can be detected or measured, respectively, by means of biochemical and pharmacological investigations. Hereinafter, some of these investigations as well as the results obtained in these investigations with characteristic compounds according to the present invention are given. The following known lipid peroxidation inhibiting compounds were used as reference substances in these biological tests: 3,5-di(tert-butyl)-4-hydroxytoluene ["butylated hydroxytoluene", BHT; see e.g. W. Snipes et al.: Science **188**, 64 (1975)]; alpha-tocopherol (Vitamin E, see e.g. the above-cited article of M. J. Kelly); 21-{4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl}-16α-methylpregna-1,4,9(11)-triene-3,20-dione [U74006F, see e.g. E. J. Jacobsen et al.: J. Med. Chem. **33**, 1145 (1990)]; as well as 2-{[4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]methyl}-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran [U78517F, see e.g. E. J. Jacobsen et al.: J. Med. Chem. **35**, 4464 (1992)].

Biochemical investigation

The inhibition of iron(II) ion dependent lipid peroxidation was measured in rat brain homogenate as described by J.M. Braughler et al. [J. Biol. Chem. **262**, 10438 (1987)] as well as by J. A. Buege and S. D. Aust [Methods in Enzymology **52**, 302 (1978)]. The IC_{50} values measured in this experiment and expressed in micromoles of several representatives of compounds according to the invention and reference compounds are shown in Table 1. The IC_{50} value is the concentration of a compound tested, which decreases by 50 % the amount of thiobarbituric acid reactive substances (first of all malondialdehyde) con-

sidered to be characteristic for the degree of lipid peroxidation.

Table 1

Compound (Example No.)	IC_{50} μM
Reference substances	
BHT	1
Vitamin E	7
U74006F	39
U78517F	0.3
Compounds of the present invention	
1	4
12	2.5
24	1.3
25	7
26	3
27	10
28	6
29	5
30	5
31	2
33	5
34	4
37	10
39	15
44	14
45	16
46	15
48	15
52	3.1

Table 1 (contd.)

Compound (Example No.)	IC_{50} μM
45	16
46	15
48	15
52	3.1
59	2
71	12
76	3.2
79	10
80	10
82	1.9
85	3.6
91	1.8
92	2.3

Pharmacological investigation

In the acute head injury test in mice described by E. D. Hall et al. [J. Neurosurg. 68, 456 (1988)], intravenous doses (given below) of representative compounds according to the invention and reference substances inhibited the brain damage (improved the neurological state of the animals) to the degree shown. The percentage of improvement is given by the change of sum of the scores characteristic for the neurological state of the animals.

Table 2

Compound (Example No.)	Dose mg/kg	Improvement %
Reference substance		
Vitamin E	30	97
U74006F	30	77

Table 2 (contd.)

Compound (Example No.)	Dose mg/kg	Improvement %
U78517F	20	31
Compounds of the present invention		
1	2.5	125
24	5	113
26	10	80
30	5	109
31	0.3	151
33	5	80
34	2.5	119
44	30	134
46	1.25	132
71	20	85
76	20	161
79	20	106
82	5	118
85	10	100
91	0.3	133
92	0.3	144

Toxicological study

The acute toxicity of compounds of the present invention was determined in rats. The toxicity of these compounds was found to be in general favourable, e.g. an intraperitoneal dose of 500 mg/kg of the compounds of Examples 31, 34 or 44, respectively, did not provoke death of any of the treated animals (LD_{50} > 500 mg/kg), similarly to the above-mentioned compound U74006F used as reference compound.

The results shown above demonstrate that several representatives of the compounds of formula (I) according to the present invention inhibit the lipid peroxidation to a significant degree under *in vitro* conditions. Consequently, as confirmed also by the above *in vivo* test results, these compounds are capable to suppress various pathological processes related to an enhanced peroxidation of lipids in the living organism. In addition, these advantageous effects are accompanied by a favourable toxicity.

For therapeutical purposes, the compounds according to the present invention and their pharmaceutically acceptable salts can be used alone or suitably in the form of pharmaceutical compositions. These compositions also fall within the scope of the present invention.

These pharmaceutical compositions contain an amount required to exert the therapeutical effect of a compound of formula (I) or its pharmaceutically acceptable salt, in admixture with known carriers, excipients, diluents and/or other additives commonly used in the pharmaceutical practice.

The doses required to exert the therapeutical effect of the compounds according to the invention may be varied depending on the individual condition and age of the patient to be treated and finally these doses are determined by the attending physician. However, for the prevention and/or treatment of diseases, where the inhibition of lipid peroxidation is desirable, daily doses of these compounds falling between about 0.1 mg/kg of body weight and about 100 mg/kg of body weight and preferably between about 1 mg/kg of body weight and about 20 mg/kg of body weight are used by the oral or parenteral, e.g. intravenous, route.

The compounds according to the invention and the process for the preparation thereof are illustrated in detail by the following non limiting Examples.

Example 1

Preparation of 1-{6-[N-(2,5-dihydroxybenzoyl)amino]-hexyl}-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

Step a)

1-{6-[N-(2,5-Dibenzyloxybenzoyl)amino]hexyl}-4-[2,6-di-(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

A mixture of 1.45 g (4.8 mmol) of 1-[2,6-di(1--pyrrolidinyl)-4-pyrimidinyl]piperazine, 3.1 g (5.7 mmol) of 6-[N-(2,5-dibenzyloxybenzoyl)amino]hexyl iodide and 0.96 g (6.9 mmol) of anhydrous potassium carbonate in 36 ml of anhydrous dimethylformamide is stirred at a temperature of 55 °C under nitrogen for 5 hours. The reaction mixture is then diluted with 120 ml of ice-water and after addition of 2 g of sodium chloride, it is extracted with ethyl acetate. The organic layer is washed with water, dried and the ethyl acetate is evaporated under reduced pressure. After washing the residue with ethyl ether, 2.47 g (72 % yield) of title compound are obtained, m.p. 131-132 °C.

Step b)

1-{6-[N-(2,5-Dihydroxybenzoyl)amino]hexyl}-4-[2,6-di(1--pyrrolidinyl)-4-pyrimidinyl]piperazine

A solution containing 2.4 g (3.3 mmol) of 1-{6-[N--(2,5-dibenzyloxybenzoyl)amino]hexyl}-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine in 120 ml of 80% aqueous ethanol is adjusted to pH 3 by adding concentrated hydrochloric acid and then hydrogenated in the presence of 1.1

g of 10% of palladium on charcoal as catalyst. After filtering off the catalyst, the pH value of the solution obtained is adjusted to 5 by using concentrated ammonium hydroxide, then the solvent is evaporated under reduced pressure. The residue is dissolved in 30 ml of water, the pH of the solution is adjusted to 8.5 with concentrated ammonium hydroxide and the mixture is extracted with chloroform. After drying the organic layer and evaporating the chloroform under reduced pressure, the residue is subjected to chromatography on a silica gel column by using ethyl acetate as eluent, the title compound is obtained in a yield of 0.76 g (43%), m.p. 182-183 °C.

Example 2

Preparation of 1-(2,6-diamino-4-pyrimidinyl)-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine

A solution containing 2.41 g (8 mmol) of 1-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine and 1.13 g (7.85 mmol) of 2,6-diamino-4-chloropyrimidine in 20 ml of chlorobenzene is stirred under reflux under nitrogen for 4 hours. After cooling, the chlorobenzene is distilled off from the precipitated, somewhat sticky material under reduced pressure. The residue is stirred with 60 ml of 2 M aqueous sodium hydroxide solution until it is disintegrated to a filtrable powder. After filtering, the solid product is washed with water until neutral and then recrystallized from ethyl acetate to obtain 1.95 g (59.5%) of title product, m.p. 165-168 °C.

Examples 3 to 10

By using appropriately substituted starting compounds and following a process similar to that described in Example 2, compounds of formula (I) are prepared, wherein

R^1 means 2-naphthyl group; and

X, A, n, R^2 and R^3 are as shown in the following Table.

Example No.	X	A	n	R^2	R^3	M.p. °C	Yield, %
3	S	$-CH_2CH(OH)CH_2-$	1	1-pyrrolidinyl	1-pyrrolidinyl	135-138	18.3
4	NH	$-CH_2CH(OH)CH_2-$	1	1-pyrrolidinyl	1-pyrrolidinyl	198-200	31.4[1]
5	NH	$-CH_2CH(OH)CH_2-$	1	NH_2	NH_2	154-159[2]	50.6
6	$N(CH_3)$	$-CH_2CH(OH)CH_2-$	1	NH_2	NH_2	85-90	42.3
7	NH	$-C(O)-CH_2-$	1	NH_2	NH_2	165-173	40.6
8	NH	$-CH_2-C(O)-$	1	NH_2	NH_2	212-215	60.0
9	S	$-CH_2-C(O)-$	1	NH_2	NH_2	185-188	89.7
10	S	$-CH_2CH(NMe_2)CH_2-$	1	NH_2	NH_2	56-62	22.9

Notes

[1] After chromatography on a silica gel column by using ethyl acetate as eluent; the product is identical to the compound of Examples 36 or 39, respectively.

[2] The reaction is carried out in the presence of 1 equivalent of sodium iodide; the product is identical to the compound of Examples 31 or 40, respectively.

[3] After recrystallization from methanol; the product is identical to the compound of Example 28.

Example 11

Preparation of 1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-hydroxy-1-naphthyl)propionyl]piperazine

A mixture containing 0.33 g (1.0 mmol) of 6-amino-2-(1-pyrrolidinyl)-4-tosyloxypyrimidine and 0.3 g (1.05 mmol) of 1-[3-(2-hydroxy-1-naphthyl)propionyl]piperazine in 20 ml of chlorobenzene is heated in a steel bomb in an oil bath at 200 - 210 °C for 10 hours, then cooled down. After evaporating the solvent, the oily residue is dissolved in 30 ml of hot methanol and after cooling down, the brown precipitate is filtered off. After evaporating

the solvent from the methanolic filtrate, the residue is subjected to chromatography on a silica gel column by using a 10:3 mixture of ethyl acetate and methanol as eluent to obtain 15 mg (3.8%) of the title compound in the form of a light brown powder, which is identical to the compound of Example 72.

Example 12

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylamino)acetyl]piperazine

A suspension of 0.70 g (4.88 mmol) of 2-naphthylamine and 1.90 g (5 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-chloroacetyl)piperazine in 70 ml of ethanol is heated under reflux for 6 hours. After distilling off the solvent under reduced pressure, the residue is stirred with a mixture of 50 ml of saturated aqueous sodium hydrogen carbonate solution and 50 ml of methylene chloride for 30 minutes. After separation the aqueous layer is extracted twice more with 50 ml of methylene chloride each, the combined organic layer is washed with 50 ml of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. After triturating the obtained crude product with 25 ml of acetonitrile under mild heating, the solids are filtered off and washed with acetonitrile to give 1.31 g (55 %) of title product, m.p. 200-220 °C.

Example 13

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(4-nitro-1-naphthylamino)acetyl]piperazine

A suspension containing 0.38 g (1.0 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-chloroacetyl)-piperazine, 0.19 g (1.0 mmol) of 4-nitro-1-naphthylamine

and 0.2 g (1.45 mmol) of potassium carbonate in 40 ml of acetonitrile is heated under reflux for 30 hours. After filtering off the insolubles, the solvent is evaporated from the filtrate under reduced pressure. By purification of the residue by chromatography on a silica gel column using a 20:1 mixture of methylene dichloride and methanol as eluent, 90 mg (17.0 %) of title product are obtained, m.p. 192-201 °C.

Example 14

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylthio)acetyl]piperazine

To a solution containing 0.64 g (4 mmol) of 2--thionaphthol in a mixture of 80 ml of ethanol and 4 ml of 1 M aqueous sodium hydroxide solution, 1.51 g (4 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-chloroacetyl)piperazine are added at room temperature. After stirring the reaction mixture at the same temperature for 2 hours and then evaporating the solvent under reduced pressure, the residue is worked up as described in Example 12. After recrystallizing the obtained crude product (2.19 g) from ethanol, 1.57 g (78.2 %) of pure title compound are obtained, m.p. 135-138 °C.

Example 15

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylthio)acetyl]homopiperazine

The title compound is prepared as described in Example 14, except that 2-thionaphthol is reacted with 1--[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-chloroacetyl)homopiperazine instead of 1-[2,6-di(1-pyrrolidinyl)--4-pyrimidinyl]-4-(2-chloroacetyl)piperazine and the crude product is stirred with 50 ml of water until it is

disintegrated to a filtrable powder to give 1.77 g (86%) of title product, m.p. 56-63 °C.

Example 16

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(2-naphthyl)carbamoylmethyl]piperazine

To a boiling suspension containing 1.2 g (4 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.68 g (5 mmol) of anhydrous potassium carbonate in 120 ml of acetonitrile, 0.86 g (4.9 mmol) of N-(2-chloroacetyl)-2-naphthylamine are added and the reaction mixture is vigorously stirred under reflux for 2 hours. After evaporating the solvent the residue is partitioned between 100 ml of water and 100 ml of methylene chloride. The aqueous phase is separated, extracted twice more with 40 ml of methylene chloride each, the combined organic layers are washed with water until neutral, dried over anhydrous magnesium sulfate, and the solvent is evaporated under reduced pressure to give 1.82 g (94.7%) of title product, m.p. 212-214 °C (after recrystallization from ethyl acetate).

Examples 17 to 23

By using appropriately substituted starting compounds and following a process similar to that described in Example 16, compounds of formula (I) are prepared, wherein

X means an NH group;

A represents a $-C(O)-CH_2-$ group;

n is 1;

both R^2 and R^3 mean 1-pyrrolidinyl group; and

R^1 has the meaning given in the following Table.

Example No.	R^1	M.p. °C	Yield %
17	2-methyl-1-naphthyl	174-176	60.5
18	1-sulfo-2-naphthyl	202-205	56.4
19	7-ethoxycarbonyl-1-naphthyl	182-185	58.7
20	7-acetyl-2-naphthyl*	oil**	98.0
21	4-(dimethylaminosulfonyl)-1--naphthyl	224-228	54.4
22	4-methylthio-1-naphthyl	219-221	61.9
23	4-methylsulfonyl-1-naphthyl	204-208	57.8

Notes

* Contains about 30% of 6-acetyl isomer.

**Thin layer chromatography R_f value is 0.70 on a Kieselgel 60 silica gel plate, eluting with a 10:3 mixture of ethyl acetate and methanol.

Example 24

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-naphthylamino)propyl]piperazine

To a solution containing 0.45 g (2.25 mmol) of N-(3--hydroxypropyl)-2-naphthylamine and 0.37 ml (0.27 g, 2.7 mmol) of triethylamine in 10 ml of anhydrous toluene a solution of 0.17 ml (0.27 g, 2.3 mmol) of methanesulfonyl chloride in 2.5 ml of anhydrous toluene is added dropwise at 0 °C over 10 minutes and the mixture is stirred at the same temperature for one hour. Subsequently, the mixture is washed with water until neutral (2 x 5 ml), dried over anhydrous magnesium sulfate, and the solvent is evaporated under reduced pressure. Thus, 0.55 g (2 mmol) of N--(3-methanesulfonyloxypropyl)-2-naphthylamine are obtained. This intermediate is dissolved in 10 ml of acetonitrile, this solution is added to a suspension containing 0.6 g (2 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyri-

midinyl]piperazine, 0.31 g (2.2 mmol) of potassium carbonate and 0.01 g of sodium iodide in 10 ml of acetonitrile, and the reaction mixture is stirred under reflux for 5 hours. After working up the reaction mixture as described in Example 13, the crude product (0.87 g) is subjected to chromatography on a silica gel column by using a 9:1 mixture of benzene and methanol as eluent to give 0.55 g (56.7%) of title product, m.p. 70-71 °C.

Example 25

Preparation of 1-[2,6-diamino-4-pyrimidinyl]-4-[2--hydroxy-3-(1-naphthylamino)propyl]piperazine

A suspension containing 2.11 g (5 mmol) of 1-(2,6--diamino-4-pyrimidinyl)piperazine bisz-trifluoroacetate and 2.07 g (15 mmol) of potassium carbonate in 100 ml of ethanol is heated under reflux while vigorously stirring for 30 minutes. After filtering off the insolubles from the hot mixture, 1.0 g (5 mmol) of N-(2,3-epoxypropyl)-1--naphthylamine dissolved in 20 ml of ethanol is added to the filtrate. After heating the reaction mixture under reflux for 3 hours and evaporating the solvent, the residue is partitioned between 100 ml of ethyl acetate and 100 ml of water. The aqueous layer is extracted with 50 ml of ethyl acetate, the combined organic solution is washed with 50 ml of saturated saline, dried over anhydrous magnesium sulfate and the solvent is distilled off. The residue is subjected to chromatography on a silica gel column by using a 2:8 mixture of benzene and methanol as eluent to obtain 0.95 g (48.4%) of title product, m.p. 105-109 °C (after trituration with ethyl ether).

Examples 26 to 37

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 25, compounds of formula (Ia) are obtained, wherein R^1, X, n, R^2 and R^3 are as shown in the following Table.

Example No.	R^1	X	n	R^2	R^3	M.p. °C	Yield, %
26	1-naphthyl	NH	1	1-pyrrolidinyl	1-pyrrolidinyl	84-85	65.6
27	1-naphthyl	NH	2	1-pyrrolidinyl	1-pyrrolidinyl	62-65	53.4
28	2-naphthyl	NH	1	NH_2	NH_2	155-158	35.8
29	2-naphthyl	NH	1	1-pyrrolidinyl	NH_2	140-142	14.5
30	2-naphthyl	NH	1	1-piperidinyl	NH_2	128-129	56.8
31	2-naphthyl	NH	1	1-pyrrolidinyl	1-pyrrolidinyl	198-201	76.0
32	2-naphthyl	$N(Ms)^{-}$	1	1-pyrrolidinyl	1-pyrrolidinyl	159-160	79.3
33	2-naphthyl	$N(CH_3)$	1	1-pyrrolidinyl	1-pyrrolidinyl	134-138	66.8
34	2-naphthyl	NH	2	1-pyrrolidinyl	1-pyrrolidinyl	103-106	71.8
35	2-naphthyl	S	1	NH_2	NH_2	158-163	35.8
36	2-naphthyl	S	1	1-pyrrolidinyl	1-pyrrolidinyl	136-140	56.6
37	2-naphthyl	S	2	1-pyrrolidinyl	1-pyrrolidinyl	83-86	61.0

Notes:

[1] Instead of ethanol, methylene chloride is used as solvent.

[2] Ms means methanesulfonyl group.

Example 38

Preparation of salts of 1-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]-piperazine

a) Salt formed with salicylic acid (salicylate)

To a solution containing 0.25 g (0.5 mmol) of 1-[2,6--di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)-propyl]piperazine base prepared according to Example 31 in 7 ml of benzene, 10 ml of 0.1 M salicylic

acid solution in ethanol are added while boiling. The mixture is allowed to cool down to room temperature, the precipitated crystalline substance is filtered off, washed with ice-cold ethanol and air-dried to give the monosalicylate of the above base, m.p. 200-206 °C; the yield of the salt formation is 77.4%.

b) Salt formed with p-toluenesulfonic acid

By following the procedure described under a) above, mono-p-toluenesulfonate of the above base is obtained with a yield of 74.7%, m.p. 173-176 °C.

c) Salt formed with phosphoric acid

By following the procedure described under a) above, diphosphate of the above base is obtained with a yield of 98.2%, which crystallizes with 2 moles of water, m.p. 260-265 °C (with decomposition).

d) Salt formed with sulfuric acid

0.25 g (0.5 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine base prepared according to Example 31 are dissolved in a mixture of 10 ml of 0.1 M aqueous sulfuric acid solution and 13 ml of ethanol under heating, then allowed to cool down. The precipitated crystals are filtered off, washed with ice-cold ethanol and air-dried to give the disulfate dihydrate of the above base, m.p. 228--230 °C (with decomposition); the yield of salt formation is 75.7%.

Example 39

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine

A solution containing 0.53 g (1.5 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2,3-epoxypropyl)-piperazine and 0.24 g (1.5 mmol) of 2-thionaphthol in 10 ml of ethanol is heated under reflux with a catalytic amount (about 0.03 ml) of triethylamine under stirring for one hour. After cooling down, the crystalline product is filtered and washed with 2 ml of cold ethyl acetate to give 0.64 g (83.1%) of title compound, which is identical to the compound of Example 3 or Example 36, m.p. 136-143 °C.

Example 40

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

The title compound is similarly prepared as described in Example 39, except that 2-naphthylamine is used instead of 2-thionaphthol and the reaction mixture is heated under reflux for 24 hours. The thus-prepared title compound is identical to the compound of Example 31. The title product is obtained in a yield of 28.7%, m.p. 198-201 °C. Alternatively, the title compound is obtained in a yield of 39.0% if about 0.05 ml of concentrated aqueous hydrochloric acid is used as catalyst instead of triethylamine.

Example 41

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-hydroxy-3-(1-naphthoylmethylamino)propyl]-piperazine

Step a)

2-{3-[4-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-2-hydroxypropyl}-2-(1-naphthyl)-1,3-dioxolane

A solution containing 0.18 g (0.5 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2,3-epoxypropyl)piperazine, 0.11 g (0.5 mmol) of 2-aminomethyl-2-(1-naphthyl)-1,3-dioxolane and 0.1 ml (0.7 mmol) of triethylamine in 5 ml of ethanol is heated under reflux for 2 hours. The solvent is distilled off under reduced pressure and the residue is dissolved in 10 ml of ethyl acetate. After washing the solution with water and drying over anhydrous magnesium sulfate, the solvent is evaporated under reduced pressure. The residue is subjected to chromatography on a silica gel column by using a 80:20 mixture of chloroform and methanol as eluent to give 0.16 g (55%) of title product, m.p. 55-60 °C.

Step b)

1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(1-naphthoylmethylamino)propyl]piperazine

The mixture containing 0.1 g (0.17 mmol) of the intermediate [prepared as described under step a) above] and 2 ml of formic acid is allowed to stand for 10 days at ambient temperature. After pouring onto 20 ml of water, the mixture is rendered alkaline to pH 10 by adding 5 N aqueous sodium hydroxide solution, the separated crystals are collected, washed with water and dried on

air. In this manner 0.06 g (65%) of title compound are obtained as a tan solid, m.p. 72-75 °C.

All 1-naphthyl compounds occurring in the present Example contain the respective 2-naphthyl isomer as a contamination in an amount of about 15 to 20% (see also Example 117).

Example 42

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-naphtoyl)piperazine

To a solution containing 0.60 g (2 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.30 ml (0.22 g, 2.2 mmol) of triethylamine in 20 ml of anhydrous methylene chloride, a solution of 0.45 g (2.2 mmol) of naphthalene-1-carboxylic acid chloride in 5 ml of anhydrous methylene chloride is added dropwise at 0 °C under stirring. After stirring at room temperature for 2 hours the reaction mixture is diluted to the twofold volume with methylene chloride. The solution is washed with water (2 x 20 ml) until neutral, dried over anhydrous magnesium sulfate, and the solvent is evaporated under reduced pressure. The crude product obtained is purified by chromatography on a silica gel column by using a 1:2 mixture of n-hexane and ethyl acetate to obtain 0.51 g (54.4 %) of title compound, m.p. 211-214 °C.

Examples 43 to 51

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 42, compounds of formula (Ib) are prepared, wherein

X and B^1 together form a single bond; and

R^1, n, R^2 and R^3 are as shown in the following Table.

Example No.	R^1	n	R^2	R^3	M.p. °C	Yield, %
43	1-naphthyl	2	1-pyrrolidinyl	1-pyrrolidinyl	188-191	61.5
44	1-hydroxy-2--naphthyl	1	1-pyrrolidinyl	1-pyrrolidinyl	215-219	50.3
45	1-hydroxy-2--naphthyl	2	1-pyrrolidinyl	1-pyrrolidinyl	110-118	38.2
46	1-hydroxy-2--naphthyl	1	1-pyrrolidinyl	NH_2	>240 (decomp.)	44.8[a]
47	1-hydroxy-2--naphthyl	1	1-piperidinyl	NH_2	170-171	26.6
48	3-hydroxy-2--naphthyl	1	1-pyrrolidinyl	1-pyrrolidinyl	231-235	36.8
49	3-hydroxy-2--naphthyl	2	1-pyrrolidinyl	1-pyrrolidinyl	239-242	72.1
50	3-hydroxy-2--naphthyl	1	1-pyrrolidinyl	NH_2	>240 (decomp.)	38.2[a]
51	3-hydroxy-2--naphthyl	1	1-piperidinyl	NH_2	171-173	28.0

Note:

[a] The reaction is performed in boiling acetonitrile.

Example 52

Preparation of 1-[6-amino-2-(hexahydro-1H-azepin-1--yl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine

Method A)

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 42, the title compound is obtained as an oil in a yield of 18%, the thin layer chromatography R_f value of which is 0.73 by developing in a 2:1 mixture of ethyl acetate and methanol on a Kieselgel 60 silica gel plate.

Method B)

After dissolving 0.19 g (1.0 mmol) of 1-hydroxy-2--naphthoic acid and 0.16 g (1.0 mmol) of carbonyldiimidazole in 20 ml of anhydrous tetrahydrofuran and stirring the reaction mixture at room temperature for one hour, 0.28 g (1.0 mmol) of 1-[6-amino-2-(hexahydro-1H-azepin-1--yl)-4-pyrimidinyl]piperazine are added, then the reaction mixture is stirred at room temperature for additional 5 hours. After evaporating the solvent, the oily residue is purified by chromatography on a silica gel column. By using a 10:2 mixture of ethyl acetate and methanol as eluent, 0.19 g (42.5%) of title product are obtained in the form of a colourless oil.

Example 53

Preparation of (-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(6-methoxy-2-naphthyl)propionyl]piperazine

To a suspension containing 2.0 g (6.61 mmol) of 1--[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 1.24 g (9 mmol) of potassium carbonate in 160 ml of dimethylformamide, an acyl chloride solution [prepared from 1.64 g (6.60 mmol) of [S-(+)-2-(6-methoxy-2-naphthyl)-propionic acid with thionyl chloride in benzene, in the presence of pyridine at room temperature] is added at 60 °C temperature during 15 minutes while stirring, then the reaction mixture is stirred at 60 °C for 4 hours. After cooling down, the reaction mixture is poured onto 750 ml of saturated aqueous sodium chloride solution. The precipitated crystals are filtered, washed with water, dried on air and subjected to chromatography on a silica gel column. By using a 9:1 mixture of chloroform and acetone as eluent 1.5 g (44.9%) of crystalline title compound are

obtained, m.p. 151-154 °C; $[\alpha]_D$ = -38.4° (c = 1, chloroform).

Examples 54 and 55

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 53, compounds of formula (I) are prepared, wherein

R^1 means 6-methoxy-2-naphthyl group;

X represents a single bond;

A stands for -CH(CH_3)-C(O)- group; and

R^2, R^3 and n are as shown in the following Table.

Example No.	R^2	R^3	n	M.p. °C	Yield, %	$[\alpha]_D^*$
54	1-pyrrolidinyl	1-pyrrolidinyl	2	84-88	76.0	-19.25°
55	NH_2	NH_2	1	122-130	38.6	-28.56°

Note:

* (c = 1, chloroform)

Example 56

Preparation of (±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(tert-butoxycarbonyl)-3-(1-naphthyl)-alanyl]piperazine

To a solution containing 0.90 g (2.9 mmol) of (±)-N--(tert-butoxycarbonyl)-3-(1-naphthyl)-alanine in 15 ml of anhydrous dimethylformamide, first 0.62 g (3 mmol) of N,N'-dicyclohexylcarbodiimide, then 0.45 g (3 mmol) of 1--hydroxybenzotriazole are added under nitrogen. After stirring for 30 minutes, a solution of 0.91 g (3 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine in 5 ml of anhydrous dimethylformamide is added. The reaction mixture is stirred at room temperature for 24 hours, then

the precipitated dicyclohexylurea is filtered off and the filtrate is poured onto 100 ml of 20% aqueous sodium chloride solution. The precipitate is filtered, washed with water, dried, washed with hexane and dried on air. After recrystallizing the crude product obtained (1.20 g, 66.7%) twice from ethanol, 0,72 g (40.0%) of pure title compound are obtained, m.p. 174-176 °C.

Examples 57 to 63

By using the appropriately substituted starting compounds and following a procedure similar to that described in Example 56, compounds of formula (Ib) are prepared, wherein

X and B^1 together form a single bond;

n is 1;

both R^2 and R^3 mean 1-pyrrolidinyl group; and

R^1 is as shown in the following Table.

Example No.	R^1	M.p. °C	Yield %
57	5-bromo-2-naphthyl	174-176	44.8
58	5,8-dibromo-2-naphthyl	193-195	50.8
59	3-methylamino-2-naphthyl	110-140(b)	15.4
60	3-dimethylamino-2-naphthyl	oil*	98.0
61	3-acetylamino-2-naphthyl	192-194	31.1
62	3-trifluoroacetylamino-2--naphthyl	196-197	59.9
63	5-cyano-2-naphthyl	210-214	77.1

Note:

*Thin layer chromatography R_f value is 0.30 on a Kieselgel 60 silica gel plate by eluting with a 10:3 mixture of ethyl acetate and methanol.

Examples 64 to 66

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 56, compounds of formula (Ib) are prepared, wherein

X represents a single bond;

B^1 means $-CH_2-CH[NH-CO-OC(CH_3)_3]-$ group;

n is 1;

both R^2 and R^3 mean 1-pyrrolidinyl group; and

R^1 is as shown in the following Table.

Example No.	R^1	M.p. °C	Yield %	$[\alpha]_D^*$
64	2-naphthyl	188-190	46.7	racemate
65	4-hydroxyphenyl	142-144	84.8	-5.87°
66	phenyl	141-144	74.4	+15.1°

Note:

(c = 1, chloroform)

Example 67

Preparation of (±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(1-naphthyl)alanyl]piperazine

A mixture containing 0.24 g (0.4 mmol) of (±)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(tert-butoxycarbonyl)-3-(1-naphthyl)alanyl]piperazine and 2 ml of 97% formic acid is stirred at room temperature for 24 hours. After pouring onto 5 ml of water under cooling by ice, the pH of the mixture is adjusted to 10 by adding 10 M sodium hydroxide solution. The formed precipitate is filtered off, washed with water, dried and then triturated with ethyl ether to obtain 0.15 g (75%) of title compound, m.p. 142-143 °C.

Examples 68 to 70

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 67, compounds of formula (Ib) are prepared, wherein

X represents a single bond;

B^1 means $-CH_2-CH(NH_2)-$ group;

n is 1;

both R^2 and R^3 mean 1-pyrrolidinyl group; and

R^1 is as shown in the following Table.

Example No.	R^1	M.p. °C	Yield %	$[\alpha]_D^*$
68	2-naphthyl	166-169	78.3	racemate
69	4-hydroxyphenyl	212-214	61.6	+14.3°
70	phenyl	180-182	88.9	+21.2°

Note:

* (c = 1, chloroform)

Example 71

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-(2-hydroxy-1-naphthyl)propionyl]piperazine

After dissolving 3.0 g (9.9 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine in 300 ml of anhydrous acetonitrile, 2.0 g (10.1 mmol) of 3-(2-hydroxy-1-naphthyl)propionic acid lactone are added under stirring. After heating under reflux for 22 hours the mixture is cooled down, the precipitate is filtered off, washed with ice-cold acetonitrile and dried on air to obtain 4.36 g (95.7%) of title compound, m.p. 274-275 °C.

Examples 72 to 74

By using appropriately substituted starting compounds and following a procedure similar to that described in

Example 71, compounds of formula (Ib) are prepared, wherein

R^1 means 2-hydroxy-1-naphthyl group;

X represents a single bond;

n is 1; and

B^1, R^2 and R^3 are as shown in the following Table.

Example No.	B^1	R^2	R^3	M.p. °C	Yield, %
72	$-CH_2-CH_2-$	1-pyrrolidinyl	NH_2	285-287[1)]	85.9
73	$-CH_2-CH_2-$	1-piperidinyl	NH_2	181-183	72.3
74	$-CH_2-$	1-pyrrolidinyl	1-pyrrolidinyl	197-198	51.4

Note:

1) Identical to the compound of Example 11.

Example 75

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(3-hydroxy-2-naphthyl)acetyl]piperazine

A solution containing 0.45 g (1.5 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.32 g (1.74 mmol) of 2-(3-hydroxy-2-naphthyl)acetic acid lactone in 50 ml of anhydrous acetonitrile is stirred at 40 °C for one hour, during this time a white precipitate appears. The mixture is cooled down, the precipitate is filtered off, washed with acetonitrile and dried on air to obtain 0.52 g (77.3%) of title compound as an off-white powder, m.p. 210-221 °C.

Example 76

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylamino)ethyl]piperazine

Method A)

The mixture of 0.14 g (1 mmol) of 2-naphthol and 0.35 g (1 mmol) of 1-(2-aminoethyl)-4-[2,6-di(1-pyrrolidinyl)--4-pyrimidinyl]piperazine is heated in a steel bomb in an oil bath at 220-225 °C for 3 hours. After cooling down, the mixture is dissolved in 20 ml of chloroform, extracted with 1 M sodium hydroxide solution, washed with saturated sodium chloride solution until neutral and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue is subjected to chromatography on a silica gel column. By using a 9:1 mixture of benzene and methanol as eluent, 0.08 g of title product are obtained, which is recrystallized from isopropanol to give the title product in a yield of 17%, m.p. 109-110 °C.

Method B)

A mixture containing 0.29 g (2 mmol) of 2-naphthol, 0.76 g (2.2 mmol) of 1-(2-aminoethyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.35 g (2 mmol) of sodium dithionite in 10 ml of water is heated in a steel bomb in an oil bath at 150-155 °C for 7 hours. After cooling down, the reaction mixture is extracted with benzene, the organic phase is washed first with 1 M aqueous sodium hydroxide solution, then with water and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue is recrystallized from isopropanol to give 0.20 g (21.3 %) of title compound in the form of a colourless crystalline product, m.p. 110-112 °C.

Method C)

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 24, first the intermediary N-(2-methanesulfonyloxyethyl)-2-naphthylamine is obtained in a yield of 50.0%, which is then reacted with 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine similarly to the procedure described in Example 24 to give the title compound in a yield of 34.1% (calculated upon the mesyloxy derivative).

Example 77

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthoylamino)ethyl]piperazine

A solution of 0.6 g (3.2 mmol) of naphthalene-2-carboxylic acid chloride in 6 ml of methylene chloride is added dropwise to a solution containing 1.0 g (2.9 mmol) of 1-(2-aminoethyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.5 ml (3.5 mmol) of triethylamine in 20 ml of methylene chloride, and the mixture is stirred without cooling for one hour. After washing the reaction mixture successively twice with 20 ml of water each, twice with 20 ml of 5% aqueous sodium hydrogen carbonate solution each and finally, twice with 20 ml of water each and drying over anhydrous magnesium sulfate, the solvent is evaporated under reduced pressure. The solid residue is triturated with acetonitrile to obtain 1.4 g (96.6%) of title compound, m.p. 221-222 °C.

Example 78

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-[2-(2-naphthyl)acetylamino]ethyl}piperazine

The title compound is prepared similarly to the procedure described in Example 77, except that 2-(2-naphthyl)acetyl chloride is used instead of naphthalene-

-2-carboxylic acid chloride, yield: 91.3%, m.p. 214-215 °C.

Example 79

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthylmethylamino)ethyl]piperazine

To 20 ml of anhydrous tetrahydrofuran, 91 mg (2.4 mmol) of lithium aluminum hydride and then 80 mg (0.6 mmol) of aluminum chloride are added. The suspension obtained is cooled to -78 °C and 0.15 g (0.3 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(2-naphthoylamino)ethyl]piperazine are added. The mixture is allowed to warm to 0 °C and stirred at the same temperature for 2 hours. Subsequently, 2 ml of water and 5 ml of a 5 M aqueous sodium hydroxide solution are added dropwise under cooling with ice. After extracting the resulting milky mixture with 20 ml of ethyl acetate, the organic phase is washed three times with 10 ml of water each until neutral, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to obtain 0.14 g (96.6 %) of crude title product as a yellow oil. The L-(+)-tartrate melts at 90-95 °C (after crystallization from ethanol).

Example 80

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-[2-(2-naphthyl)ethylamino]ethyl}piperazine

The title compound is prepared by using 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-[2-(2-naphthyl)acetylamino]ethyl}-piperazine as starting substance and following a procedure similar to that described in Example 79. The title compound is obtained in a yield of 55.2 %, the L-(+)-tartrate salt melts at 105-115 °C (after crystallization from ethanol).

Example 81

Preparation of 1-[2-acetoxy-3-(N-acetyl-2-naphthylamino)propyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

After dissolving 0.17 g (0.34 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine in 3 ml of acetic anhydride by heating to about 50 °C, the solution is allowed to stand at room temperature for 2 hours, then poured onto water. After dissolution of the excess acetic anhydride, the mixture is extracted three times with 10 ml of chloroform each. The combined organic solution is washed three times with water, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. After triturating the oily residue with water, 0.16 g of solids are obtained. This product is subjected to chromatography on a silica gel column. By using a 9:1 mixture of methylene chloride and methanol as eluent, the title product is obtained in a yield of 0.13 g (65.0%), m.p. 70-75 °C.

Example 82

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-methoxy-3-(2-naphthylamino)propyl]piperazine

To 10 ml of anhydrous dimethylsulfoxide, 33 mg (1.1 mmol) of 80% sodium hydride are added under nitrogen, and the mixture is stirred at room temperature for 30 minutes. Then, 0.5 g (1 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]-piperazine are added and the mixture is stirred for additional 30 minutes. After adding 0.1 ml (0.23 g, 1.6 mmol) of methyl iodide to the suspension and stirring the reaction mixture for an additional hour, a yellow solution is formed. The dimethylsulfoxide solution is extracted three

times with 10 ml of ethyl ether each, the combined ethereal solution is washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. The oily residue (0.42 g) is subjected to chromatography on a silica gel column by using ethyl acetate as eluent to obtain 0.16 g (31.1%) of title product as a colourless gum, which solidifies upon standing, m.p. 33-38 °C. This compound has a thin layer chromatography R_f value of 0.5 on a Kieselgel 60 silica gel plate, by eluting with ethyl acetate.

Example 83

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(N-ethoxycarbonyl-2-naphthylamino)propyl]piperazine

A suspension containing 0.50 g (1 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine in 15 ml of anhydrous pyridine is cooled to -5 °C temperature and 0.15 ml (0.17 g, 1.56 mmol) of ethyl chloroformate are added. The mixture is stirred at 0 °C for one hour, during this time the suspension is transformed to a yellow solution. After pouring the reaction mixture onto 100 ml of water and extracting three times with 50 ml of ethyl ether each, the combined organic layers are washed twice with 50 ml of water each, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to give 0.47 g (82.8%) of title product, m.p. 70-77 °C.

Example 84

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(ethoxycarbonyloxy)-3-(2-naphthylamino)-propyl]piperazine

To a suspension containing 0.50 g (1 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine in 20 ml of anhydrous methylene chloride, 0.27 ml (0.30 g, 1.85 mmol) of diethyl dicarbonate are added at 0 °C under stirring. The mixture is stirred at the same temperature for one hour and then at room temperature for 16 hours, whereupon the insoluble materials are dissolved. After evaporating the solvent, the residue is purified by chromatography on a silica gel column. By using an 1:4 mixture of hexane and ethyl acetate as eluent, 0.40 g (69.8%) of title compound is obtained, m.p. 63-68 °C.

Example 85

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-(tert-butoxycarbonyloxy)-3-(2-naphthylamino)propyl]piperazine

To a suspension containing 0.95 g (1.9 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine in 20 ml of anhydrous methylene chloride, 0.36 ml (0.19 g, 1.9 mmol) of triethylamine, 0.23 g (1.9 mmol) of 4-dimethylaminopyridine and 0.83 g (3.8 mmol) of di(tert-butyl)dicarbonate are added. After stirring the reaction mixture at room temperature for 8 hours and then allowed to stand overnight in the refrigerator, the insolubles are filtered off and the solvent is evaporated from the filtrate under reduced pressure. The residue is purified by chromatography on a silica gel column by using an 1:4 mixture of hexane and

ethyl acetate as eluent to obtain 0.32 g (28.3%) of title product, m.p. 82-84 °C.

Example 86

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(7-carboxy-1-naphthyl)carbamoylmethyl]piperazine

A solution of 0.20 g (3.56 mmol) of potassium hydroxide in 2 ml of ethanol is added to a suspension containing 0.4 g (0.7 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[N-(7-ethoxycarbonyl-1-naphthyl)carbamoylmethyl]piperazine in 10 ml of ethanol and the reaction mixture is heated under reflux for one hour while stirring. After evaporating the solvent under reduced pressure, the residue is subjected to chromatography on a silica gel column by using an 1:1 mixture of benzene and methanol as eluent to give the potassium salt of the title product in a yield of 0.16 g (41.0 %), m.p. above 360 °C.

Example 87

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(5-carboxamido-2-naphthoyl)piperazine

To 3 g of polyphosphoric acid stirred in an oil bath at 110-115 °C 0.1 g (0.2 mmol) of 1-(5-cyano-2-naphthoyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine is added, and the reaction mixture is stirred at the same temperature for one hour. After cooling to about 60 °C, the mixture is poured onto 20 ml of ice-water. The aqueous solution is rendered alkaline by adding 5 N sodium hydroxide solution, the precipitate is filtered, washed with water and then with acetonitrile to obtain 0.09 g (90%) of title product, m.p. 280 °C (with decomposition).

Example 88

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylsulfinyl)propyl]piperazine

To a solution containing 0.58 g (1.12 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylthio)propyl]piperazine in 5 ml of acetic acid cooled in an ice bath, 0.35 ml of a 30 % aqueous hydrogen peroxide solution are added, then the mixture is allowed to stand at room temperature for 60 hours. After diluting with 20 ml of water, the mixture is neutralized by adding a saturated sodium hydrogen carbonate solution while stirring in an ice bath. Subsequently, the mixture is extracted three times with 40 ml of chloroform each, the combined organic solution is washed with 30 ml of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. The residue is subjected to chromatography on a silica gel column by using a 4:1 mixture of ethyl acetate and methanol as eluent to give 0.12 g (20.0%) of title compound, m.p. 184-186 °C.

Example 89

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

The solution of 0.5 g (0.86 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-{2-hydroxy-3-[N-methanesulfonyl-N-(2-naphthyl)amino]propyl}piperazine in 15 ml of anhydrous tetrahydrofuran is added dropwise to a suspension containing 1.0 g (26.4 mmol) of lithium aluminum hydride in 50 ml of anhydrous tetrahydrofuran at room temperature during 20 minutes and the reaction mixture is stirred at the same temperature for 2 hours. Then, successively 10

ml of ethyl acetate, 10 ml of water and finally, 20 ml of 10 N aqueous sodium hydroxide solution are added while cooling with ice. After separation, the aqueous phase is extracted three times with 20 ml of ethyl acetate each. The combined organic layers are washed with water until neutral (3 x 20 ml), dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. After triturating the solid residue with acetonitrile, 0.27 g (62.8%) of title product are obtained as a tan powder, which is identical to the product of Example 31, m.p. 188-190 °C.

Example 90

Preparation of 1-(3-amino-2-naphthoyl)-4-[2,6-di(1--pyrrolidinyl)-4-pyrimidinyl]piperazine

To a solution containing 0.29 g (0.51 mmol) of 1--[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[3-trifluoroacetylamino-2-naphthoyl]piperazine in 20 ml of anhydrous tetrahydrofuran, 2 ml of 4% aqueous sodium hydroxide solution are added and the mixture is heated under reflux for 8 hours under vigorous stirring, then allowed to stand at room temperature overnight. After evaporation of the solvent, the oily residue is triturated with water, the solidified product is filtered, washed with water and dried on air. Thus, the title compound is obtained in a yield of 0.21 g (77.8%) as a white powder, m.p. 223-224 °C.

Example 91

Preparation of (-)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

Method A)

A solution containing 1.02 g (7.1 mmol) of 2--naphthylamine and 0.73 g (0.62 ml, 7.9 mmol) of S-(+)--epichlorohydrin in the mixture of 10 ml of ethanol and 2.4 ml of water is stirred under reflux for 3 hours. After evaporating the solvent under reduced pressure, three times 10 ml of ethanol each are evaporated from the residue. Thus, 1.78 g (7 mmol) of the corresponding crude chlorohydrin, namely N-(2-hydroxy-3-chloropropyl)-2-naphthylamine are obtained, which is used without further purification in the next reaction step.

A suspension containing the above chlorohydrin, 2.1 g (7 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and 1.8 g (13 mmol) of potassium carbonate in 40 ml of acetonitrile is heated under reflux under vigorous stirring for 5 hours. After evaporating the solvent under reduced pressure and triturating the residue with the mixture of 50 ml of water and 100 ml of ethanol while boiling, the suspension obtained is cooled to room temperature, the precipitate is filtered off, washed with water until neutral and dried on air. Thus, 1.4 g of title product are obtained, which is boiled with 140 ml of a 1:1:1 mixture of ethanol, ethyl acetate and acetonitrile for a few minutes. After cooling down, the purified product is filtered, washed with the above solvent mixture and dried on air to obtain 2.1 g (59.0%) of title compound, m.p. 217-221 °C; $[\alpha]_D$ = -4.4° (c = 2, in a 1 M aqueous hydrochloric acid solution).

Method B)

Step a)

(+)-N-(2,3-Epoxypropyl)-2-naphthylamine

A solution containing 1.02 g (7.1 mmol) of 2-naphthylamine and 0.73 g (0.62 ml, 7.9 mmol) of S-(+)-epichlorohydrin in the mixture of 10 ml of ethanol and 2.4 ml of water is stirred under reflux for 3 hours. After evaporating the solvent under reduced pressure, three times about 10 ml of ethanol each are evaporated from the residue. Thus, 1.78 g (7 mmol) of the corresponding chlorohydrin, namely N-(2-hydroxy-3-chloropropyl)-2-naphthylamine are obtained which is used without further purification in the next reaction step.

To the solution of the above crude chlorohydrin in the mixture of 3.5 ml of anhydrous methanol and 1.6 ml of anhydrous ethyl ether, 0.25 g (10.87 mmol) of sodium metal is added in three equal portions at a temperature between 0 °C and 5 °C during 15 minutes. After stirring the reaction mixture at 0 °C for one hour, the solvent is distilled off under reduced pressure, the residue is subjected to chromatography on a silica gel column by using a 96:4 mixture of benzene and methanol as eluent to give 0.52 g of crystalline title compound, which is washed with isopropyl ether, filtered and dried on air. According to thin layer chromatography this product is not completely pure. The yield is 0.53 g (37.4%), m.p. 119-121 °C; $[\alpha]_D$ = +16.4° (c = 1, chloroform).

Step b)

(-)-1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

A solution containing 0.39 g (1.95 mmol) of (+)-N-(2,3-epoxypropyl)-2-naphthylamine and 0.57 g (1.90 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine in

30 ml of ethanol is stirred under reflux for 2 hours. After cooling down, the crystalline precipitate is filtered off, washed with ice-cold ethanol and dried on air to give 0.70 g (73.4%) of title product, m.p. 220-221 °C; $[\alpha]_D$ = -4.5° (c = 2, in a 1 M aqueous hydrochloric acid solution).

Example 92

Preparation of (+)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

Method A)

Method A) of Example 91 is followed, except that R-(-)-epichlorohydrin is used instead of S-(+)-epichlorohydrin to give 1.9 g (53.4%) of title product, m.p. 216-219 °C; $[\alpha]_D$ = +4.3° (c = 2, in a 1 M aqueous hydrochloric acid solution).

Method B)

Step a)

(-)-N-(2,3-Epoxypropyl)-2-naphthylamine

Step a) of method B) of Example 91 is followed, except that R-(-)-epichlorohydrin is used instead of S-(+)-epichlorohydrin to obtain 0.50 g (35.3%) of title compound, m.p. 116-118 °C; $[\alpha]_D$ = -22.8° (c = 1, chloroform).

Step b)

(+)-1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine

Step b) of method B) of Example 91 is followed, except that (-)-N-(2,3-epoxypropyl)-2-naphthylamine described in step a) of method B) of the present Example is used instead of (+)-N-(2,3-epoxypropyl)-2-naphthylamine to obtain 0.58 g (60.8%) of title compound, m.p. 218-220

°C; $[\alpha]_D$ = +4,4° (c = 2, in a 1 M aqueous hydrochloric acid solution).

The preparation of novel intermediates used in the above Examples 1 to 92 is illustrated in Examples 93 to 117 described hereinbelow.

Example 93

Preparation of 1-[2-hydroxy-3-(2-naphthylamino)-propyl]piperazine

Step a)

N-(2,3-Epoxypropyl)-2-naphthylamine

A solution containing 5.16 g (36 mmol) of 2--naphthylamine and 4.4 g (3.7 ml, 47.5 mmol) of epichlorohydrin in the mixture of 12 ml of ethanol and 6 ml of water is heated under reflux for 3 hours while stirring. After cooling down, the mixture is diluted with water to a volume of 100 ml and extracted three times with 30 ml of ethyl acetate each. The combined organic phase is washed with water, dried over anhydrous magnesium sulfate and the solvent is distilled off. After stirring the residue with 100 ml of ethyl ether and 20 ml of 10 M aqueous sodium hydroxide solution for 2 hours, the organic phase is separated, washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is distilled off. The residue is subjected to chromatography on a silica gel column by using a 95:5 mixture of benzene and methanol as eluent to obtain 4.33 g of product which is triturated with isopropyl ether to give the title compound in a yield of 60.3%, m.p. 101-102 °C.

By using appropriately substituted starting compounds and following a procedure similar to that described in the above step a), the oily compounds of formula (VIII) are prepared, wherein

R^1 and X are as shown in the following Table.

Example No.	R^1	X	$Rf^{1)}$	Yield %
94-a)	1-naphthyl	NH	0.76	70.7
95-a)	2-naphthyl	$N(CH_3)$	0.85	45.0
96-a)	2-naphthyl	S	0.90	85.7

Note:

1) Thin layer chromatography R_f values on Kieselgel 60 silica gel plates by eluting with a 95:5 mixture of benzene and methanol.

Step b)

1-[2-Hydroxy-3-(2-naphthylamino)propyl]-4-(tert-butoxycarbonyl)piperazine

Method A)

A solution containing 1.47 g (7.35 mmol) of N-(2,3-epoxypropyl)-2-naphthylamine [prepared as described in step a) above] and 1.38 g (7.4 mmol) of 1-(tert-butoxycarbonyl)piperazine in 30 ml of ethanol is heated under reflux for 2 hours. After distilling off the alcohol, the crystalline residue obtained is washed with ethyl acetate to give 1.97 g (65.9%) of title compound, m.p. 131-132 °C.

Method B)

A mixture containing 1.21 g (5 mmol) of 1-(2,3-epoxypropyl)-4-(tert-butoxycarbonyl)piperazine, 0.59 g (4.2 mmol) of 2-naphthylamine and 20 ml of ethanol is heated under reflux for 15 hours. After distilling off the solvent, the crude product obtained is subjected to chromatography on a silica gel column by using ethyl acetate as eluent to obtain 0.89 g (55.3 %) of title compound.

Compounds of formula (XIV), wherein

A means 2-hydroxy-1,3-propylene group;

n is 1;

R^4 stands for a tert-butoxycarbonyl group; and

R^1 and X are as shown in the following Table,

are prepared similarly to the procedures described in the above methods A) or B), respectively.

Example No.	R^1	X	Method	Rf[1)]	Yield %
94-b)	1-naphthyl	NH	A	0.71	67.5
95-b)	2-naphthyl	$N(CH_3)$	A	0.69	90.0
96-b)	2-naphthyl	S	B	0.78	80.7

Note:

[1)] Thin layer chromatography R_f value on Kieselgel 60 silica gel plates by eluting with a 95:5 mixture of benzene and methanol.

Step c)

1-[2-Hydroxy-3-(2-naphthylamino)propyl]piperazine

To 1.85 g (4.79 mmol) of 1-[2-hydroxy-3-(2-naphthylamino)propyl]-4-(tert-butoxycarbonyl)piperazine [prepared by using any of the methods of step b) above] 6 ml of trifluoroacetic acid cooled to 0 °C are added and the mixture is stirred for 90 minutes while maintaining the temperature at 0 °C. After distilling off the excess acid under reduced pressure, twice 10 ml of anhydrous ethyl ether each are evaporated from the residue. The crystalline product obtained is dissolved in 30 ml of water, the solution is rendered alkaline by adding 10 M aqueous sodium hydroxide solution under stirring and cooling, then the mixture is extracted 4 times with 30 ml of ethyl acetate each. After washing the combined ethyl acetate layers with 40 ml of water and drying over anhydrous magnesium sulfate, the solvent is evaporated to obtain 0.67 g (45.9%) of crystalline title compound, m.p. 142-144 °C.

By following the procedure described in step c) above, compounds of formula (II) are prepared, wherein

A means 2-hydroxy-1,3-propylene group;

n is 1; and

R^1 and X are as shown in the following Table.

Example No.	R^1	X	M.p. °C[1)]	Yield %
94-c)	1-naphthyl	NH	112-117	61.3
95-c)	2-naphthyl	$N(CH_3)$	oil[2)]	76.1
96-c)	2-naphthyl	S	130-133	98.0

Notes:

1) Bis-trifluoroacetate salts.

2) Thin layer chromatography R_f value is 0.58 on a Kieselgel 60 silica gel plate, by eluting with a 75:20:5 mixture of ethyl acetate, methanol and concentrated aqueous ammonium hydroxide solution.

Example 97

Preparation of 1-[2-dimethylamino-3-(2-naphthylthio)-propyl]piperazine

A solution of 0.45 ml (0.66 g, 5.7 mmol) of mesyl chloride in 5 ml of methylene chloride is added dropwise to a solution containing 1.7 g (4.2 mmol) of 1-[2-hydroxy-3-(2-naphthylthio)propyl]-4-(tert-butoxycarbonyl)piperazine and 0.87 ml (0.64 g, 63 mmol) of triethylamine in 30 ml of methylene chloride at a temperature between 20 and 25 °C. After stirring the mixture for one hour, an additional 0.87 ml of triethylamine and 0.45 ml of mesyl chloride are added and the mixture is stirred for an additional hour. Subsequently, it is washed three times with 15 ml of water each, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. Thus, 2.32 g of crude 1-[2-methane-

sulfonyloxy-3-(2-naphthylthio)propyl]-4-(tert-butoxycarbonyl)piperazine are obtained (in a yield over 100 %) in the form of a yellow oil, which is used without further purification in the next reaction step.

A mixture containing the above crude methanesulfonyloxy derivative and 20 ml of 33% ethanolic dimethylamine solution is allowed to stand at room temperature for 48 hours, then the volatile components are evaporated under reduced pressure. After partitioning the residue between 30 ml of water and 30 ml of ethyl acetate, the aqueous layer is separated and extracted twice with 15 ml of ethyl acetate each. The combined organic solution is extracted three times with 15 ml of 1 N hydrochloric acid each, then the pH of the combined aqueous-acidic solution is adjusted to 10 by adding a 5 N sodium hydroxide solution and extracted three times with 20 ml of ethyl acetate each. The organic layers obtained in the latter extraction are combined, washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. Thus, 1.46 g of crude 1-[2-dimethylamino-3-(2-naphthylthio)propyl]-4-(tert-butoxycarbonyl)piperazine are obtained in the form of a yellow oil (in a yield of 81.1% calculated upon the starting hydroxy compound), which is used without further purification in the next reaction step.

After dissolving the above crude, protected dimethylamino compound in 20 ml of 10% aqueous hydrochloric acid and stirring the solution at room temperature for one hour, the solution is washed three times with 10 ml of ethyl acetate each, then the aqueous-acidic phase is adjusted to pH 10 by adding a 5 N sodium hydroxide solution and extracted three times with 20 ml of ethyl acetate each. The organic phases obtained in the latter extraction are combined, washed with water until neutral, dried

over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. By purifying the obtained crude product (0.87 g) through its salt formed with L-(+)-tartaric acid [m.p. 40-45 °C (after crystallization from ethanol)], 0.66 g of title product are obtained as a thick, light yellow oil having a thin layer chromatography R_f value of 0.30 (on a Kieselgel 60 silica gel plate, by eluting with a 20:11:6:30 mixture of pyridine, water, acetic acid and ethyl acetate). The overall yield of the three reaction steps is 47.8% calculated upon the starting hydroxy compound.

Example 98

Preparation of 1-[3-(2-hydroxy-1-naphthyl)propionyl]-piperazine

Step a)

1-[3-(2-Hydroxy-1-naphthyl)propionyl]-4-(tert-butoxy-carbonyl)piperazine

To the solution of 0.85 g (5.0 mmol) of 1-(tert-butoxycarbonyl)piperazine in 75 ml of anhydrous acetonitrile 1.0 g (5.04 mmol) of 3-(2-hydroxy-1-naphthyl)-propionic acid lactone is added and the solution is heated under reflux for 4 hours. After evaporation of the solvent 1.85 g (97%) of title compound are obtained as a colourless oil, which is used without further purification in the next reaction step.

Step b)

1-[3-(2-Hydroxy-1-naphthyl)propionyl]piperazine

Upon dissolving 0.37 g (1.0 mmol) of 1-[3-(2-hydroxy-1-naphthyl)propionyl]-4-(tert-butoxycarbonyl)piperazine under stirring at room temperature in 10 ml of a 16% solution of hydrogen chloride in ethyl acetate fine particles of a white precipitate appear after a few minutes.

After stirring for one hour the precipitate is filtered off, washed with a small amount of ethyl acetate and dried at room temperature. The dried product is dissolved in 5 ml of 5% sodium hydrogen carbonate solution while stirring. The base form of the product precipitates from the solution in the form of a white solid within a short time. After stirring the mixture for additional 10 minutes, the precipitate is filtered off, washed with a small volume of cold water and dried on air to give 0.31 g (99%) of title product, m.p. 107-109 °C.

Example 99

Preparation of 1-[2-(2-naphthylamino)acetyl]piperazine

Step a)

1-(2-Chloroacetyl)-4-(tert-butoxycarbonyl)piperazine

The solution of 0.88 ml (1.24 g, 11 mmol) of 2-chloroacetyl chloride in 10 ml of anhydrous chloroform is added dropwise to a solution containing 1.86 g (10 mmol) of 1-(tert-butoxycarbonyl)piperazine and 1.53 ml (1.11 g, 11 mmol) of triethylamine in 50 ml of anhydrous chloroform at 0 °C temperature under stirring. The reaction mixture is stirred at room temperature for an additional hour, washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to give 1.91 g (72.9%) of title compound, m.p. 91-93 °C.

Step b)

1-[2-(2-Naphthylamino)acetyl]-4-(tert-butoxycarbonyl)piperazine

A suspension containing 0.78 g (3 mmol) of 1-(2-chloroacetyl)-4-(tert-butoxycarbonyl)piperazine, 0.43 g (3 mmol) of 2-naphthylamine and 0.42 g (3 mmol) of potassium carbonate in 30 ml of acetonitrile is heated under

reflux for 8 hours under vigorous stirring. Then, the solvent is distilled off and the residue is partitioned between 30 ml of methylene chloride and 30 ml of water. The organic phase is washed three times with 10 ml of water each, dried over anhydrous magnesium sulfate and the solvent is distilled off to give 1.03 g of crude product which is subjected to chromatography on a silica gel column by using an 1:1 mixture of n-hexane and ethyl acetate as eluent to yield 0.34 g (30.9%) of crystalline title product, m.p. 190-192 °C.

Step c)

1-[2-(2-Naphthylamino)acetyl]piperazine

The title compound is prepared by starting from the compound prepared as described in the preceding step b) and following the procedure described in step c) of Example 93. The trifluoroacetate salt melts at 102-108 °C; a yield of 85.3% is achieved.

Example 100

Preparation of 1-[2-(2-naphthylthio)acetyl]piperazine

Step a)

1-[2-(2-Naphthylthio)acetyl]-4-(tert-butoxycarbonyl)-piperazine

A mixture containing 0.48 g (3 mmol) of 2-thionaphthol, 70 ml of ethanol, 3 ml of 1 N aqueous sodium hydroxide solution and 0.78 g (3 mmol) of 1-(2-chloroacetyl)-4-(tert-butoxycarbonyl)piperazine (prepared as described under step a) of Example 100 above) is stirred at room temperature for 2 hours. After evaporating the solvent under reduced pressure, the residue is partitioned between 30 ml of methylene chloride and 30 ml of water. The organic solution is washed with water until neutral, dried over anhydrous magnesium sulfate and the

solvent is evaporated under reduced pressure to give 0.66 g (58.6%) of title product, m.p. 80-82 °C.

Step b)

1-[2-(2-Naphthylthio)acetyl]piperazine

The title compound is prepared by starting from the compound prepared as described in the preceding step a) and following the procedure described under step c) of Example 93. The product is obtained as an oil with a thin layer chromatography R_f value of 0.64 (on a Kieselgel 60 silica gel plate, by eluting with a 75:20:5 mixture of ethyl acetate, methanol and concentrated aqueous ammonium hydroxide solution) in a yield of 96.8%.

Example 101

Preparation of 1-[N-(2-naphthyl)carbamoylmethyl]piperazine

Step a)

1-[N-(2-Naphthyl)carbamoylmethyl]-4-(tert-butoxycarbonyl)piperazine

A mixture containing 1.48 g (8 mmol) of 1-(tert-butoxycarbonyl)piperazine, 1.36 g (9.8 mmol) of powdered potassium carbonate and 1.76 g (8 mmol) of N-(2-chloroacetyl)-2-naphthylamine in 60 ml of acetonitrile is heated under reflux for 2 hours while stirring. After evaporating the solvent, the residue is partitioned between 60 ml of methylene chloride and 60 ml of water. The organic phase is washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is distilled off. The crude product is subjected to chromatography on a silica gel column by using an 1:2 mixture of n-hexane and ethyl acetate as eluent to yield 2.05 g (69.5%) of crystalline title product, m.p. 124-128 °C.

Step b)

1-[N-(2-Naphthyl)carbamoylmethyl]piperazine

The title compound is prepared by starting from the compound prepared as described in the preceding step a) by following the procedure described in step c) of Example 93. The product is identified in the form of its bis--trifluoroacetate salt, m.p. 169-175 °C. A yield of 80.6% is achieved.

Example 102

Preparation of 1-[6-amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

Step a)

1-Amidinopyrrolidine hydroiodide

To a solution of 174.32 g (0.8 mol) of S-methylisothiourea hydroiodide in 600 ml of methanol, 60.53 g (70.2 ml, 0.85 mol) of pyrrolidine are added while stirring. The reaction mixture is heated under reflux for 3 hours until ceasing of the gas evolution. After cooling down and evaporating the solvent, the residue is recrystallized from methanol to yield 169.3 g (87.9%) of title product, m.p. 192-193 °C.

Step b)

6-Amino-4-hydroxy-2-(1-pyrrolidinyl)pyrimidine

After dissolving 8.1 g (0.35 mol) of sodium metal in 240 ml of anhydrous methanol under stirring, 72.3 g (0.3 mol) of 1-amidinopyrrolidine hydroiodide are added to the obtained solution. In an other flask 8.1 g of sodium metal are dissolved in 240 ml of anhydrous methanol and 34.2 g (0.3 mol) of ethyl cyanoacetate are dissolved in this latter solution. The mixture obtained is added to the solution prepared above. The reaction mixture is stirred under reflux for 3 hours and then cooled down.

After evaporating the solvent under reduced pressure, the residue is dissolved in 150 ml of water and the solution is acidified to pH 5 by adding acetic acid while stirring. The white precipitate is filtered off, washed several times with water and dried on air to obtain 39.0 g (71.0%) of title product, m.p. 264-266 °C.

Step c)

6-Amino-2-(1-pyrrolidinyl)-4-tosyloxypyrimidine

To a suspension containing 3.6 g (20 mmol) of 6--amino-4-hydroxy-2-(1-pyrrolidinyl)pyrimidine in 20 ml of pyridine, 5.0 g (25 mmol) of tosyl chloride are added at room temperature. The reaction mixture is stirred at room temperature for 30 minutes, during this time the starting compounds are dissolved. Then, the reaction mixture is poured onto 100 ml of water whereupon the product is precipitated in solid form. The precipitate is filtered off, washed with a large volume of water and dried on air to yield 3.0 g (45%) of title product, m.p. 155-168 °C (with decomposition).

Step d)

1-[6-Amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

The mixture of 17.0 g (50.9 mmol) of 6-amino-2-(1--pyrrolidinyl)-4-tosyloxypyrimidine, 150 ml of chlorobenzene and 15 g (175 mmol) of anhydrous piperazine is heated in a steel bomb in an oil bath at 140-145 °C for 4 hours. Next day, the crystalline precipitate (excess of piperazine) is filtered off, washed with a small volume of chlorobenzene and the solvent is distilled off from the combined chlorobenzene filtrate and washings. The residue is dissolved in 15 ml of methanol and the solution is acidified to pH 6 by adding ethyl acetate containing hydrogen chloride. The crystalline precipitate is

filtered, washed with ethyl acetate and dried. The hydrochloride obtained (m.p. above 280 °C) is dissolved in a small volume of water, made alkaline to pH 10 by adding 1 M sodium hydroxide solution and the product is extracted into methylene chloride (3 x 100 ml). After combining the organic phases, the solution is dried over anhydrous magnesium sulfate and the solvent is distilled off to give 3.7 g (30%) of title product as a light yellow oil, which solidifies upon standing.

Example 103

Preparation of 1-[6-amino-2-(1-piperidinyl)-4-pyrimidinyl]piperazine

Step a)

1-Amidinopiperidine hydroiodide

The title compound is prepared as described in step a) of Example 102, except that piperidine is used instead of pyrrolidine to give a yield of 72.3%, m.p. 118-120 °C.

Step b)

6-Amino-4-hydroxy-2-(1-piperidinyl)pyrimidine

The title compound is prepared starting with the compound obtained as described in the preceding step a) and by following the procedure described in step b) of Example 102 to give a yield of 97.3%, m.p. 182-192 °C (with decomposition).

Step c)

6-Amino-2-(1-piperidinyl)-4-chloropyrimidine

A mixture containing 7.29 g (37.6 mmol) of 6-amino-4-hydroxy-2-(1-piperidinyl)pyrimidine and 37.5 ml of phosphorus oxychloride is stirred at 100 °C for 2 hours, then the excess of phosphorus oxychloride is distilled off under reduced pressure. After mixing the residue with a

twofold volume of water, the viscous yellow oil is dissolved after a few minutes with violent warming and gas evolution. The solution is made alkaline by adding a 10% aqueous sodium carbonate solution up to pH 8 and cooling down. The crystalline precipitate is filtered off, washed with water until neutral and dried on air to give a yield of 73.3% of the title product, m.p..: 148-149 °C.

Step d)

1-[6-Amino-2-(1-piperidinyl)-4-pyrimidinyl]piperazine

The tile compound is prepared starting with the compound prepared as described in the preceding step c) and by following the procedure described in step d) of Example 102 to give a yield of 66.7%. The product is a yellow oil having a thin layer chromatography R_f value of 0.3 (on a Kieselgel 60 silica gel plate, by eluting with a 10:5:0.3 mixture of ethyl acetate, methanol and concentrated aqueous ammonium hydroxide solution).

Example 104

Preparation of 1-[6-amino-2-(hexahydro-1H-azepin-1-yl)-4-pyrimidinyl]piperazine

Step a)

6-Amino-2-(hexahydro-1H-azepin-1-yl)-4-chloropyrimidine

After dissolving 6.56 g (40 mmol) of 6-amino-2,4-dichloropyrimidine in 200 ml of anhydrous dimethylformamide under stirring and adding 4.2 g (4.8 ml, 43 mmol) of hexamethylene imine, the reaction mixture is stirred at room temperature for 24 hours, then 8 ml of anhydrous pyridine are added and the mixture is stirred at the same temperature for additional 24 hours. After distilling off the solvent under reduced pressure, the white solid residue is extracted with a 10:2 hot mixture of chloroform and

methanol (2 x 100 ml). After evaporating the solvent from the extract under reduced pressure, the residue is subjected to chromatography on a silica gel column by using a 20:1 mixture of chloroform and methanol as eluent to obtain 1.97 g (21.7%) of title compound as a white powder, m.p. 152-154 °C.

Step b)

6-Amino-2-(hexahydro-1H-azepin-1-yl)-4-[4-(tert-butoxycarbonyl)-1-piperazinyl]pyrimidine

A solution containing 1.97 g (8.68 mmol) of 6-amino-2-(hexahydro-1H-azepin-1-yl)-4-chloropyrimidine and 5.55 g (32.6 mmol) of 1-(tert-butoxycarbonyl)piperazine in 55 ml of anhydrous chlorobenzene is heated under reflux for 24 hours while stirring under dry nitrogen. Subsequently, a little amount of solid precipitate is filtered off and the solvent is evaporated from the filtrate under reduced pressure. The residue is subjected to chromatography on a silica gel column by using ethyl acetate as eluent to give 3.05 g (97.0%) of title product as a light yellow oil with a thin layer chromatography R_f value of 0.48 (on a Kieselgel 60 silica gel plate, by eluting with a 10:2 mixture of ethyl acetate and methanol).

Step c)

1-[6-Amino-2-(hexahydro-1H-azepin-1-yl)-4-pyrimidinyl]piperazine

After dissolving 2.92 g (8.1 mmol) of the compound prepared as described in the preceding step b) in 20 ml of anhydrous ethyl acetate while stirring, 10.8 ml of a 16% m/v solution of hydrogen chloride in ethyl acetate are added under stirring. A white substance immediately begins to precipitate from the solution. The mixture is stirred at room temperature for one hour, then the pre-

cipitate is filtered off, washed with ethyl acetate and dried on air. The dry intermediate is dissolved in 30 ml of distilled water and rendered alkaline to pH 9 by adding a 4% aqueous sodium hydroxide solution. After extracting the oily precipitate into methylene chloride, the organic phase is dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to yield 1.13 g (50.5%) of title compound as a yellow powder, m.p. 122-124 °C.

Example 105

Preparation of N-(2,3-epoxypropyl)-N-methanesulfonyl--2-naphthylamine

To the solution of 0.5 g (2.5 mmol) of N-(2,3-epoxypropyl)-2-naphthylamine in 5 ml of anhydrous pyridine, 0.24 ml (0.35 g, 3.0 mmol) of methanesulfonyl chloride is added dropwise while stirring and cooling in an ice bath, then the mixture is stirred in an ice bath for one hour. Subsequently, 0.24 ml of methanesulfonyl chloride is again added and the stirring is continued at the same temperature for 2 hours. After allowing to warm to ambient temperature the mixture is poured onto water. The precipitate is filtered, washed with water and recrystallized from methanol to obtain 0.37 g (52.9%) of title compound as a pale yellow crystalline product, m.p. 114--115 °C.

Example 106

Preparation of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2,3-epoxypropyl)piperazine

A solution containing 1.5 g (5 mmol) of 1-[2,6-di(1--pyrrolidinyl)-4-pyrimidinyl]piperazine and 0.5 ml (0.59 g, 6.4 mmol) of epichlorohydrin in 10 ml of ethanol is stirred at ambient temperature for 24 hours. The precipi-

tate is filtered off and washed with 2 ml of ethanol. The wet material is dissolved in the mixture of 50 ml of ethyl ether and 5 ml of ethanol and stirred with 10 ml of a 10 M aqueous sodium hydroxide solution for 2 hours. After separation, the organic layer is washed with water until neutral, dried over anhydrous magnesium sulfate and the solvent is distilled off to yield 1.18 g (66.4%) of crystalline title substance, m.p. 107-112 °C.

Example 107

Preparation of 1-(2-aminoethyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

Step a)

1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-phthalimidoethyl)piperazine

A suspension containing 6.04 g (20 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine, 6.35 g (25 mmol) of N-(2-bromoethyl)phthalimide, 3.45 g (25 mmol) of potassium carbonate and 3.0 g (20 mmol) of sodium iodide in 100 ml of acetonitrile is heated under reflux for 3 hours while stirring. After cooling down the reaction mixture in ice bath, the solids are filtered off and washed first with acetonitrile and then with a large volume of water to give 6.03 g of crude product. The solvent is distilled off from the acetonitrile filtrate under reduced pressure and the residue is subjected to chromatography on a silica gel column by using ethyl acetate as eluent. Thus, 2.2 g of a not completely pure product are obtained, which is combined with the above crude product of 6.03 g (yield 86.2%) and recrystallized first from acetonitrile and then from isopropanol. Thus, 4.85 g (51.0%) of title product are obtained as yellow crystals, m.p. 153-154 °C.

Step b)

1-(2-Aminoethyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

4.25 g (8.9 mmol) of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-4-(2-phthalimidoethyl)piperazine are dissolved in 100 ml of ethanol at 60-70 °C, 4.6 ml (90 mmol) of 98% hydrazine hydrate are added and the reaction mixture is heated under reflux for one hour. After cooling down, the precipitated phthaloylhydrazide is filtered off, washed with ethanol, then the solvent is evaporated from the filtrate under reduced pressure. To the residue 15 ml of methylene chloride are added and a little amount of insoluble phthaloylhydrazide is filtered off. The filtrate is washed with water, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to yield 2.91 g (94.8%) of title compound as a colourless powder, m.p. 99-100 °C.

Example 108

Preparation of N-(2-chloroacetyl)-2-methyl-1-naphthylamine

To a solution of 0.5 g (3.18 mmol) of 2-methyl-1-naphthylamine in 5 ml of N,N-dimethylacetamide, 0.3 ml (0.45 g, 4.0 mmol) of 2-chloroacetyl chloride are added at ambient temperature under stirring. After 30 minutes, the solvent is evaporated under reduced pressure and the residue is recrystallized from 5 ml of isopropanol to give 78.0% of title product, m.p. 177-178 °C.

Examples 109 to 113

By using appropriately substituted starting compounds and following a procedure similar to that described in Example 108, compounds of formula (VI) are prepared, wherein

X means NH group;

A represents $-C(O)-CH_2-$ group;

Z means chlorine; and

R^1 is as shown in the following Table.

Example No.	R^1	M.p. °C	Yield %
109	7-ethoxycarbonyl-1-naphthyl	173-175	59.4
110	7-acetyl-2-naphthyl*	117-122	99.0
111	2-sulfo-1-naphthyl	145-146	94.4
112	4-methylthio-1-naphthyl	186-188	98.0
113	4-methylsulfonyl-1-naphthyl	181-182	99.0

Note:

* Contains about 30% of 6-acetyl isomer.

Example 114

Preparation of 4-(dimethylaminosulfonyl)-N-(2-chloroacetyl)-1-naphthylamine

To the solution of 0.63 g (2 mmol) of N-(2-chloroacetyl)-4-chlorosulfonyl-2-naphthylamine in 50 ml of tetrahydrofuran, 0.5 ml (4 mmol) of 40% aqueous dimethylamine solution are added dropwise at ambient temperature. The mixture is stirred for 30 minutes, then the solvent is evaporated under reduced pressure and an additional 5 ml of ethanol are distilled off from the residue. The residue is triturated with hot ethyl acetate and kept in the refrigerator overnight. Next day, the solid product is filtered off to obtain 0.58 g (89.2%) of title compound, m.p. 186-190 °C.

Example 115

Preparation of 6-[N-(2,5-dibenzyloxybenzoyl)amino]-hexyl iodide

Step a)

6-[N-(2,6-Dibenzyloxybenzoyl)amino]hexylalcohol

To a solution containing 15.1 g (33.7 mmol) of 6-[N--(2,5-dibenzyloxybenzoyl)amino]hexanoic acid in the mixture of 390 ml of anhydrous tetrahydrofuran and 3.4 g (33.7 mmol) of anhydrous triethylamine, the solution of 3.65 g (33.7 mmol) of distilled ethyl chloroformate in 17 ml of anhydrous tetrahydrofuran is added dropwise at -5 °C temperature while stirring, then the reaction mixture is stirred at the same temperature for 30 minutes. The precipitated salt is filtered off and washed with anhydrous tetrahydrofuran. The combined filtrate and washings are added portionwise to the solution of 3.1 g (82 mmol) of sodium borohydride in 78 ml of water at a temperature of 15 °C under stirring during 30 minutes, then the reaction mixture is stirred at ambient temperature for 4 hours. After adjusting the pH of the solution to 4 by adding 5 M hydrochloric acid solution and stirring the mixture at ambient temperature for 3 hours, if required, the pH of the solution is again adjusted to 4 as mentioned above. Then, 240 ml of water and 240 ml of ethyl ether are added to the solution, the aqueous layer is separated and extracted with a 6:1 mixture of ethyl ether and tetrahydrofuran. The organic layers are combined, washed with water and 5% sodium hydroxide solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue is washed with petroleum ether (b.p. 40-70 °C) to give 11.7 g (80%) of title compound, m.p. 90-92 °C.

Step b)

6-[N-(2,5-Dibenzyloxybenzoyl)amino]hexyl iodide

To a solution containing 3.44 g (7.9 mmol) of 6-[N-(2,5-dibenzyloxybenzoyl)amino]hexylalcohol in the mixture of 24 ml of anhydrous methylene chloride and 1.2 g (12 mmol) of anhydrous triethylamine, 1.1 g (9.6 mmol) of methanesulfonyl chloride are added at 0 °C while stirring and the reaction mixture is stirred at 0 °C for 30 minutes. Subsequently, 24 ml of water are added and after separation the aqueous layer is extracted with methylene chloride. The organic solution is briefly dried over anhydrous magnesium sulfate, the solvent is evaporated under reduced pressure and the residue is stirred under reflux in 25 ml of acetone saturated with sodium iodide, in the presence of 0.09 g (0.7 mmol) of diisopropylethylamine under nitrogen for 30 minutes. After diluting the reaction mixture with 25 ml of water and extraction with ethyl ether, the ethereal solution is dried over anhydrous magnesium sulfate, the solvent is evaporated under reduced pressure and the residue obtained is washed with petroleum ether (b.p. 40-70 °C) to yield 3.83 g (89%) of title compound, m.p. 80-82 °C.

Example 116

Preparation of 3-trifluoroacetylamino-2-naphthoic acid

After boiling under reflux a mixture consisting of 1.87 g (10 mmol) of 3-amino-2-naphthoic acid and 10 ml of trifluoroacetic acid anhydride for 3 hours, the mixture is cooled down, the solid precipitate is filtered, washed with trifluoroacetic acid anhydride and ethyl ether and dried over phosphorus pentoxide under reduced pressure, Thus, 1.93 g (68.2%) of title compound are obtained as a white powder, m.p. 133-134 °C.

Example 117

Preparation of 2-aminomethyl-2-(1-naphthyl)-1,3-dioxolane

Step a)

2-Azidomethyl-2-(1-naphthyl)-1,3-dioxolane

To a solution containing 2.04 g (10 mmol) of 1-(2-chloroacetyl)naphthalene in 20 ml of dimethylformamide, 1.3 g (20 mmol) of sodium azide are added under cooling by ice water and the mixture is stirred without cooling for one hour. The deep red suspension obtained is diluted with 60 ml of water and extracted three times with 40 ml of benzene each. The combined organic solution is washed with water, dried over anhydrous magnesium sulfate, decolorized with about 5 g of silica gel and the solvent is distilled off under reduced pressure. Thus, 1.82 g (86.3%) of 1-(2-azidoacetyl)naphthalene are obtained as an orange yellow oil, which is used without further purification in the next reaction step.

To the emulsion of the above azido compound in 22 ml of anhydrous ethylene glycol, 4.3 ml (2.84 g, 26.1 mmol) of chlorotrimethylsilane are added dropwise under nitrogen at ambient temperature and the mixture is stirred for 2 hours. At this time, an additional amount of 2.15 ml of chlorotrimethylsilane is added and the stirring is continued for one hour. After extracting the solution obtained three times with 40 ml of hexane each, the combined hexane solution is washed with 5% aqueous sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. Thus, 1.36 g (61.8%) of title compound are obtained as a lemon yellow oil, which solidifies upon standing, m.p. 30-35 °C.

Step b)

2-Aminomethyl-2-(1-naphthyl)-1,3-dioxolane

To a solution containing 0.37 g (1.45 mmol) of the intermediate obtained as described in the preceding step a) in 10 ml of ethanol, 0.05 g (0.2 mmol) of nickel chloride hexahydrate and subsequently 0.29 g (5.8 mmol) of sodium borohydride are added. After stirring for 10 minutes, the pH of the mixture is adjusted to 7 by adding 1 N hydrochloric acid, the black precipitate is filtered off and the ethanol is removed from the filtrate under reduced pressure. After triturating the residue with water, a little amount of insoluble material is filtered off, and the filtrate is rendered alkaline by adding concentrated aqueous ammonium hydroxide solution and extracted three times with 10 ml of ethyl acetate each. The combined organic solution is washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. Thus, 0.17 g of title compound is obtained as a yellow oil, which solidifies upon standing, m.p. 94-95 °C (after triturating with isopropyl ether). The yield is 51.5%.

All 1-naphthyl compounds occurring in the present Example contain as contamination about 15-20% of the respective 2-naphthyl isomer. During preparation of chloroacetylnaphthalene used as starting substance in step a), a mixture of 1- and 2-naphthyl isomer is namely formed, in agreement with the literature data [see Y. Murakami: Chem. Pharm. Bull. 36, 2023 (1988)].

Example 118

Intravenous pharmaceutical formulation

Ingredients

1-{6-[N-(2,5-Dihydroxybenzoyl)-amino]-hexyl}-4-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]piperazine dihydrochloride	5.00 g
Sodium chloride	4.00 g
Water for injection q.s.	ad 1000.00 ml

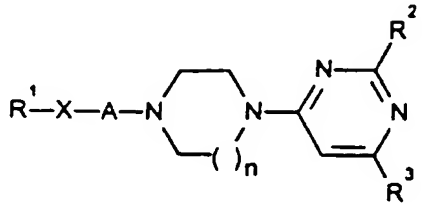
Preparation:

After dissolving the pyrogen-free 1-{6-[N-(2,5-dihydroxybenzoyl)amino]hexyl}-4-[2,6-di(1-pyrrolidinyl)-4--pyrimidinyl]piperazine dihydrochloride and the sodium chloride in 800 ml of distilled water for injection, the volume of the solution is supplemented with distilled water for injection up to 1000.00 ml.

Subsequently, the solution is filtered germ-free through a cellulose membrane of 0.2 µm pore diameter, filled into glass ampoules under aseptic conditions and the ampoules are sealed in an inert gas atmosphere.

Claims

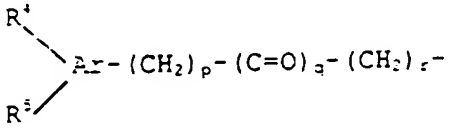
1. Compounds of the formula (I),



(I)

wherein

R^1 stands for a moiety of formula (a)



(a)

wherein

Ar means a C_{6-10} aromatic homocyclic group,

R^4 and R^5, independently from each other, represent hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, nitro, C_{1-4} alkanoyl, optionally substituted amino, carboxy, C_{1-4} alkoxycarbonyl, carboxamido, cyano, sulfo and/or sulfonamido; and

p, q, and r are, independently from each other, 0 or 1;

R^2 and R^3, independently from each other, stand for amino; or a moiety derived from a 5-8-membered saturated heterocycle containing at least one nitrogen atom;

X means a single bond; a sulfur atom optionally substituted by one or two oxygen atom(s) or an optionally substituted nitrogen atom;

A stands for a straight or branched chain C_{1-8} alkylene group optionally substituted by halogen, hydroxy, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} al-

kanoyloxy, optionally substituted amino and/or oxo; and

n is 1 or 2,

with the proviso that when

R^1 means a moiety of formula (a), wherein

Ar means phenyl; and

at least one of R^4 and R^5 stands for halogen, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-4} alkanoyloxy or methanesulfonyloxy;

A may not be unsubstituted C_{1-4} alkylene; and

with the further proviso that when

R^1 is 2,5-dihydroxybenzoyl;

A may not be alkylene substituted by oxo;

as well as their pure stereoisomers, mixtures of stereoisomers and addition salts, especially pharmaceutically acceptable salts formed with acids or bases of these compounds.

2. 1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine and acid-addition salts thereof.

3. (+)-1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine and acid-addition salts thereof.

4. (-)-1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]piperazine and acid-addition salts thereof.

5. 1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine and acid-addition salts thereof.

6. (+)-1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine and acid-addition salts thereof.

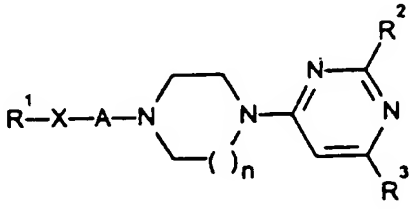
7. (-)-1-[2,6-Di(1-pyrrolidinyl)-4-pyrimidinyl]-4-[2-hydroxy-3-(2-naphthylamino)propyl]homopiperazine and acid-addition salts thereof.

8. 1-[6-Amino-2-(1-pyrrolidinyl)-4-pyrimidinyl]-4-(1-hydroxy-2-naphthoyl)piperazine and salts thereof.

9. 1-{6-[N-(2,5-Dihydroxybenzoyl)amino]hexyl}-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine and salts thereof.

10. Pharmaceutical composition, which comprises as active ingredient a compound of formula (I), wherein R^1, R^2, R^3, X, A and n are as defined in claim 1, or a pharmaceutically acceptable salt thereof in admixture with solvents, diluents, carriers, excipients and other additives commonly used in the pharmaceutical practice.

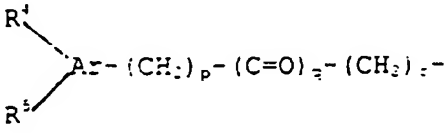
11. Process for the preparation of pyrimidine derivatives of formula (I),



(I)

wherein

R^1 stands for a moiety of formula (a)



(a)

wherein

Ar means a C_{6-10} aromatic homocyclic group,

R^4 and R^5, independently from each other, represent hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, nitro, C_{1-4}

alkanoyl, optionally substituted amino, carboxy, C_{1-4} alkoxycarbonyl, carboxamido, cyano, sulfo and/or sulfonamido; and

p, q, and r are, independently from each other, 0 or 1;

R^1 and R^3, independently from each other, stand for amino; or a moiety derived from a 5-8-membered saturated heterocycle containing at least one nitrogen atom;

X means a single bond; a sulfur atom optionally substituted by one or two oxygen atom(s) or an optionally substituted nitrogen atom;

A stands for a straight or branched chain C_{1-8} alkylene group optionally substituted by halogen, hydroxy, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkanoyloxy, optionally substituted amino and/or oxo; and

n is 1 or 2,

with the proviso that when

R^1 means a moiety of formula (a), wherein

Ar means phenyl; and

at least one of R^4 and R^5 stands for halogen, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-4} alkanoyloxy or methanesulfonyloxy;

A may not be unsubstituted C_{1-4} alkylene; and

with the further proviso that when

R^1 is 2,5-dihydroxybenzoyl;

A may not be alkylene substituted by oxo;

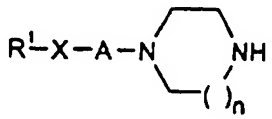
which comprises that

a) in order to obtain compounds of formula (I), wherein

R^1, R^2, R^3, X and n are as defined above; and

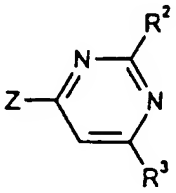
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino,

a compound of formula (II),



(II)

wherein R^1, X, A and n are as defined above, is reacted with a compound of formula (III),



(III)

wherein R^2 and R^3 are as defined above and Z means a leaving group; or

b) in order to obtain compounds of formula (I), wherein R^1, R^2, R^3 and n are as defined above;

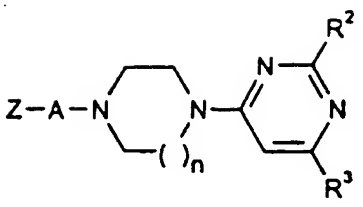
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino; and

X is as defined for the formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atom(s),

a compound of formula (IV),

$$R^1\text{-}XH \qquad \text{(IV)}$$

wherein R^1 and X are as defined above, is reacted with a compound of formula (V),



(V)

wherein R^2, R^3, A and n are as defined above and Z means a leaving group; or

c) in order to obtain compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above;

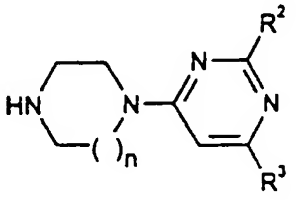
A is as defined above, with the proviso that it may not be alkylene substituted by halogen, amino or C_{1-4} alkylamino; and

X is as defined above, with the proviso that it may not be a single bond,

a compound of formula (VI),

$$R^1\text{-}X\text{-}A\text{-}Z \qquad (VI)$$

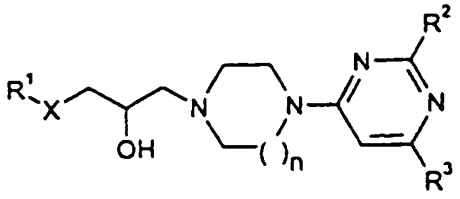
wherein R^1, X and A are as defined above and Z means a leaving group, is reacted with a compound of formula (VII),



(VII)

wherein R^2, R^3 and n are as defined above; or

d) in order to obtain compounds of formula (Ia)



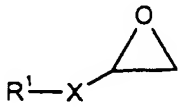
(Ia)

representing a narrower scope of compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above; and

X is as defined above, with the proviso that it may not be a single bond,

a compound of formula (VIII),



(VIII)

wherein R^1 and X are as defined above, is reacted with a compound of formula (VII), wherein

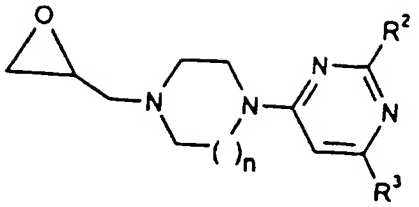
R^2, R^3 and n are as defined above; or

e) in order to obtain compounds of formula (Ia) representing a narrower scope of the compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above; and

X is as defined for formula (I), with the proviso that it may not be a single bond or a sulfur atom substituted by one or two oxygen atom(s),

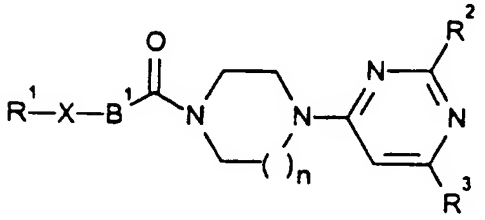
a compound of formula (IV), wherein R^1 and X are as defined above, is reacted with a compound of formula (IX),



(IX)

wherein R^2, R^3 and n are as defined above; or

f) in order to obtain compounds of formula (Ib)



(Ib)

representing a narrower scope of compounds of formula (I), wherein

R^1, R^2, R^3, X and n are as defined above; and

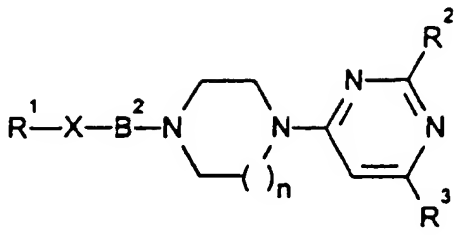
B^1 means a single bond or a straight or branched chain C_{1-3} alkylene group optionally substituted by halogen, C_{1-4} alkoxy, C_{1-4} alkanoyloxy and/or an optionally substituted amino group,

a carboxylic acid of formula (X),

$$R^1\text{-}X\text{-}B^1\text{-}COOH \qquad (X)$$

wherein R^1, X and B^1 are as defined above, or a reactive derivative thereof activated at the carboxyl group is reacted with a compound of formula (VII), wherein R^2, R^3 and n are as defined above; or

g) in order to obtain compounds of formula (Ic)



(Ic)

representing a narrower scope of the compounds of formula (I), wherein

R^1, R^2, R^3 and n are as defined above;

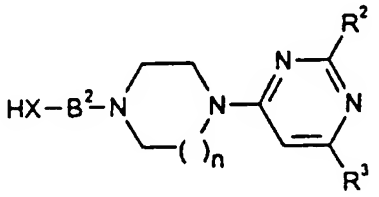
X stands for a nitrogen atom optionally substituted by a C_{1-4} alkyl group; and

B^2 means a straight or branched chain C_{2-3} alkylene group optionally substituted by hydroxy, C_{1-4} alkoxy and/or di(C_{1-4} alkyl)amino group,

a compound of formula (XI),

$$R^1\text{-}Z \qquad (XI)$$

wherein Z means a leaving or hydroxyl group and R^1 is as defined above, with the proviso that p, q and r are 0 when Z means a hydroxyl group, is reacted with a compound of formula (XII),



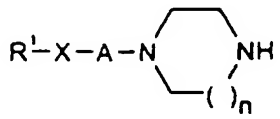
(XII)

wherein R^2, R^3, B^2, X and n are as defined above,

and, if desired, a compound of formula (I) obtained by using any of the process variants a) to g) is transformed to an other compound of formula (I) in a manner known *per se*; and/or a protective group optionally being present is removed; and/or, if desired, a compound of formula (I)

thus prepared is resolved; and/or transformed to the salt form, e.g. acid-addition salt thereof.

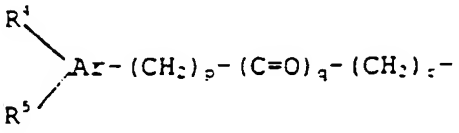
12. Compounds of the formula (II),



(II)

wherein

R^1 stands for a moiety of formula (a),



(a)

wherein

Ar means a C_{6-10} aromatic homocyclic group;

R^4 and R^5, independently from each other, represent hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy optionally substituted by phenyl, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, nitro, C_{1-4} alkanoyl, optionally substituted amino, carboxyl, C_{1-4} alkoxycarbonyl, carboxamido, cyano, sulfo and/or sulfonamido; and

p, q and r are, independently from each other, 0 or 1;

R^2 and R^3, independently from each other, stand for amino; or a moiety derived from a 5 to 8-membered saturated heterocycle containing at least one nitrogen atom;

X means a single bond; a sulfur atom optionally substituted by one or two oxygen atom(s); or an optionally substituted nitrogen atom;

A stands for a straight or branched chain C_{1-8} alkylene group optionally substituted by halogen, hydroxy, C_{1-4}

alkoxy optionally substituted by phenyl, C_{1-4} alkanoyloxy, optionally substituted amino and/or oxo group; and

n is 1 or 2,

with the proviso that when

R^1 means a moiety of formula (a), wherein

Ar means phenyl; and

at least one of R^4 and R^5 stands for halogen, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-4} alkanoyloxy or methanesulfonyloxy;

A may not be unsubstituted C_{1-4} alkylene; and

with the further proviso that when

R^1 is 2,5-dihydroxybenzoyl;

A may not be alkylene substituted by oxo.

INTERNATIONAL SEARCH REPORT

Intr onal Application No
PCT/HU 96/00058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/50 C07D295/12 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 574 906 (NISSHIN FLOUR MILLING) 22 December 1993 cited in the application see the whole document ---	1,10,11
A	EP,A,0 576 941 (NISSHIN FLOUR MILLING) 5 January 1994 cited in the application see claims; examples 21,35 -----	1,10,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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1

Date of the actual completion of the international search	Date of mailing of the international search report
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